ORGANIC SYNTHESES

I

ACETYL BENZOIN

$$C_6H_5CHOHCOC_6H_5 + (CH_3CO)_2O \rightarrow C_6H_5CH(OCOCH_3)COC_6H_5 + CH_3CO_2H$$

Submitted by B. B. CORSON AND N. A. SALIANI.
Checked by FRANK C. WHITMORE and MARION M. WHITMORE.

1. Procedure

To a mixture of 212 g. (1 mole) of benzoin (Note 1), 200 cc. of glacial acetic acid and 200 cc. (2.1 moles) of acetic anhydride in a 1-l. beaker provided with a mechanical stirrer, is added slowly, with stirring, 20 cc. of concentrated C.P. sulfuric acid. This requires five minutes, during which the benzoin quickly dissolves and the temperature rises to about 50°. The beaker is placed on the steam bath for twenty minutes (Note 2). The mixture is allowed to cool somewhat, transferred to a large dropping funnel and added *slowly* to 2500 cc. of water vigorously stirred in a 4-l. (1-gal.) crock during thirty minutes (Note 3). The stirring is continued for one hour. The mixture is filtered by suction on a 30-cm. Büchner funnel. The crystals are sucked as dry as possible and spread on filter paper. After about two hours the crystals are transferred to a 1-l. beaker and warmed to about 60° with 400 cc. of 95 per cent ethyl alcohol. The clear solution is cooled with stirring to 5° and filtered by suction. The air-dried acetyl benzoin, melting at 80–82°, weighs 220–230 g. (86 to 90 per cent of the theoretical

amount). Another crystallization from 400 cc. of alcohol removes the slight yellow tinge and gives a product melting at 81.5–82.5°, with a loss of about 10 g.

2. Notes

1. The benzoin (Org. Syn. **1**, 33) need not be recrystallized.

2. The mixture should not be heated longer or more vigorously.

3. If the product solidifies in lumps, these must be removed, crushed to a paste in a large mortar and returned to the mixture for stirring.

3. Methods of Preparation

The only method of preparative interest is the acetylation of benzoin, either with acetyl chloride [1] or with acetic anhydride.[2] The melting point of acetyl benzoin was reported by Zinin as "below 100°," by Jena and Limpricht as 75° but by later investigators as 82–83°.

[1] Zinin, Ann., **104**, 120 (1857); Jena and Limpricht, Ann., **155**, 92 (1870); Papcke, Ber., **21**, 1336 (1888).

[2] Francis and Keane, J. Chem. Soc., **99**, 346 (1911).

II

d-ARGININE HYDROCHLORIDE

$$\text{Gelatine} \xrightarrow{\text{Hydrolysis}} \text{Amino Acids}$$

$$NH_2C(NH)NHCH_2CH_2CH_2CH(NH_2)CO_2H + C_6H_5CHO \rightarrow$$
$$NH_2C(NH)NHCH_2CH_2CH_2CH(NCHC_6H_5)CO_2H \cdot H_2O$$

$$C_{13}H_{18}O_2N_4 \cdot H_2O + HCl \rightarrow$$
$$NH_2C(NH)NHCH_2CH_2CH_2CH(NH_2HCl)CO_2H + C_6H_5CHO$$

Submitted by E. Brand and M. Sandberg.
Checked by H. T. Clarke and S. Graff.

1. Procedure

Benzylidenearginine, Method 1. To 500 g. of gelatine (Note 1) is added 1500 cc. of concentrated hydrochloric acid (sp. gr. 1.19); the mixture is warmed on the steam bath for thirty minutes and boiled over a free flame for eight to ten hours (Note 2) under a reflux condenser provided with a trap for hydrogen chloride gas (Note 3). The solution is then concentrated to 400 cc. on the steam bath under reduced pressure, employing the apparatus shown in Org. Syn. **4**, 54. The syrupy residue is then diluted with 500 cc. of distilled water and again concentrated to 400 cc. This process of dilution and evaporation is repeated twice more (Note 4). The final residue is dissolved in 500 cc. of hot distilled water and decolorized by adding 15 g. of decolorizing carbon and heating for ten minutes on the steam bath. The filtrate is chilled in an ice-salt bath and treated with 250–350 cc. of a 40 per cent solution of sodium hydroxide until slightly alkaline to litmus, keeping the temperature below 10°. An additional 70-cc. portion of 40 per cent sodium hydroxide solu-

tion is added, keeping the temperature below 5°; this is followed by the addition, in four portions, of 225 cc. of benzaldehyde, with vigorous shaking after each addition, the temperature being held below 5° throughout (Note 5). The addition of the benzaldehyde occupies about ten minutes.

The resulting emulsion is allowed to stand overnight in the refrigerator at 0–5°; the crystalline precipitate is filtered off by suction and washed first with 80 cc. of ice-cold water in four portions, then with 50 cc. of a mixture of two volumes of ether and one volume of methyl alcohol, and finally with ether (Note 6) until the washings are colorless and free of benzaldehyde. After drying in a vacuum desiccator the product weighs 35–40 g. (60–68 per cent of the theoretical amount); it melts with decomposition at 206–207° (corr.).

Benzylidenearginine, Method 2. The hydrolysis of 500 g. of gelatine and the removal of excess hydrochloric acid are conducted as described above. After treatment with 15 g. of decolorizing carbon the filtrate is diluted to 2500 cc., heated almost to boiling and treated with 110 g. of 2,4-dinitro-1-naphthol-7-sulfonic ("flavianic") acid (Note 7) dissolved in 400 cc. of hot water. The mixture is boiled (Note 8) for about three minutes and diluted with boiling water to a total volume of 4 l. The mixture is cooled rapidly to 45° and then allowed to cool slowly to room temperature, with occasional stirring and vigorous scratching of the walls of the container. After standing for about two hours at room temperature (Note 9), practically all (Note 10) of the arginine dinitronaphtholsulfonate should have separated in crystalline, readily filterable form. The product is filtered off by suction and washed first with 300 cc. of a 0.5 per cent solution of dinitronaphtholsulfonic acid in three portions and then with 50 cc. of 95 per cent ethyl alcohol in two portions. After being dried in air the product weighs 113–118 g. (Note 11); it decomposes at 245–265° (Note 12).

One hundred grams (0.21 mole) of finely powdered arginine dinitronaphtholsulfonate is added, all at once, to 230 cc. of cold 2 *N* sodium hydroxide; the salt dissolves readily on agitation. There is then added *without delay* (Note 13) 35 g. (0.33

mole) of benzaldehyde, in four portions and with vigorous shaking, each portion being accompanied by 75 cc. of ice-cold water. During this process, benzylidenearginine separates as a crystalline cake. The mixture is allowed to stand at 15–20° for one to two hours, whereupon the product is filtered off (Note 14) and washed successively with two to four 50-cc. portions of ice-cold water, three 20-cc. portions of a mixture of 20 cc. of methyl alcohol and 40 cc. of ether, and finally two 50-cc. portions of ether (Note 6). It is then dried in air. The yield is 39–43 g. (66–73 per cent of the theoretical amount), corresponding to about 44–48 g. from 500 g. of gelatine (Note 11).

Arginine Hydrochloride. A suspension of 50 g. (0.18 mole) of benzylidenearginine in 39 cc. of 5 N hydrochloric acid is heated in a boiling water or steam bath for forty-five minutes, with occasional shaking. The mixture is allowed to cool and is freed of benzaldehyde by shaking with three 100–150 cc. portions of ether. The aqueous solution is filtered if necessary, decolorized with 3 g. of decolorizing carbon, filtered, and concentrated on the water bath at 70° under reduced pressure until crystallization sets in. The residue is transferred from the flask with the aid of 25 cc. of hot 70 per cent ethyl alcohol; the arginine hydrochloride is precipitated by adding 300 cc. of absolute alcohol. After filtering off the product, a further small quantity of crystalline hydrochloride is obtained by adding 300 cc. of ether to the mother liquor. The combined (Note 15) yield amounts to 33–34 g. (88–90 per cent of the theoretical amount). It melts at 220° (corr.) and exhibits a rotation of $[\alpha]_D^{25°} = +12.2$ to 12.3° (5 per cent in water).

2. Notes

1. The quality of gelatine is technically defined on the basis of its physical properties, and different samples vary widely in chemical composition. In checking, the highest yields (9.7–10.3 per cent of the weight of gelatine taken) of benzylidenearginine were secured from the "Bactogelatine" of the Digestive Ferments Company.

2. The biuret reaction is generally found to be negative after five hours.

3. A tube is led from the top of the reflux condenser to an inverted funnel placed with the wide end a short distance above a surface of cold water.

4. The third distillate generally contains only 1–2 g. of hydrogen chloride. In checking this preparation on a larger scale, it has been found convenient to add the water continuously below the surface of the boiling syrup; this modification, which constitutes a steam distillation under reduced pressure, brings about a more rapid removal of the excess hydrochloric acid.

5. Unless the temperature is held below 5°, difficulty is experienced in emulsifying the benzaldehyde.

6. Benzylidenearginine is quite insoluble in ether but appreciably soluble in methyl alcohol and in water. Attempts to recrystallize it from the latter solvents lead to a product of inferior quality, owing to decomposition in solution. Impure or contaminated samples may be purified by hydrolysis with hot hydrochloric acid and reprecipitation with benzaldehyde after neutralization.

7. The free dinitronaphtholsulfonic acid can be prepared readily from commercial Naphthol Yellow S by treating a filtered saturated solution of the dye with three volumes of concentrated hydrochloric acid. The crystals which separate are washed with cold 20 per cent hydrochloric acid and dried, first in air and finally in a vacuum desiccator over solid sodium hydroxide.

8. The boiling prevents the precipitation of arginine diflavianate and minimizes the separation of the flavianates of other amino acids.

9. Crystallization is occasionally delayed, particularly in first runs when traces of arginine flavianate are not available in the atmosphere for spontaneous inoculation. In such cases it may be necessary to chill the solution in the refrigerator with occasional vigorous scratching.

10. The mother liquor, on long standing in the ice box, may deposit a second crop of crystals which appear to consist largely

of sodium dinitronaphtholsulfonate and yield no arginine on further treatment. The filtrate thus obtained in Method 2 is suitable for the recovery of other amino acids, thereby differing from the corresponding mother liquor from Method 1.

11. This yield was obtained from a batch of gelatine from which 35–36 g. of benzylidenearginine was obtained by Method 1.

12. According to the literature,[2] pure arginine dinitronaphtholsulfonate melts at 258–260° with decomposition. Presence of moisture lowers the melting point considerably. If the mother liquor be allowed to stand for several days at 0–5°, some sodium dinitronaphtholsulfonate may crystallize out.

13. Delay in adding the benzaldehyde must be avoided or sodium dinitronaphtholsulfonate may crystallize out; the water is added to prevent this. The presence of the excess of benzaldehyde also appears to be of assistance in this prevention.

14. A sintered-glass suction filter is advantageous for collecting and washing the benzylidenearginine.

15. The over-all loss involved in the various steps may be estimated from the following experiment: 5.0 g. of arginine nitrate was converted through the dinitronaphtholsulfonate into benzylidenearginine and then back into arginine nitrate, when 4.2 g. was recovered.

3. Methods of Preparation

Arginine has been precipitated (*a*) in the form of its silver derivative at *p*H 10;[1] (*b*) as its dinitronaphtholsulfonate which is then decomposed by means of 33 per cent sulfuric acid,[2] by the combined action of hot dilute sulfuric acid and butyl alcohol,[3] by cold concentrated hydrochloric acid followed by aniline,[4] or by barium hydroxide.[5] Arginine has likewise been precipitated

[1] Kossel, Z. physiol. Chem. **22**, 176 (1896–7); **25**, 165 (1898); Kossel and Kutscher, Z. physiol. Chem. **31**, 165 (1900); Vickery and Leavenworth, J. Biol. Chem. **72**, 403 (1927); **75**, 115 (1927).

[2] Kossel and Gross, Z. physiol. Chem. **135**, 167 (1924).

[3] Pratt, J. Biol. Chem. **67**, 351 (1926).

[4] Cox, J. Biol. Chem. **78**, 475 (1928).

[5] Felix and Dirr, Z. physiol. Chem. **176**, 38 (1928).

(*c*) in the form of its benzylidene derivative from solutions rendered alkaline with barium hydroxide or sodium hydroxide.[6] It has been separated as such (*d*) from protein hydrolysates by electrolysis under controlled *p*H.[7]

In the present directions, Method 1 is essentially that developed by Bergmann and Zervas;[6] Method 2 forms a combination of methods (*b* and *c*) and thus at once affords a product of high purity, while avoiding the mechanical difficulties involved in the complete removal of the dinitronaphtholsulfonic acid from its arginine salt.

[6] Bergmann and Zervas, Z. physiol. Chem. **152**, 282 (1926); **172**, 277 (1927).

[7] Foster and Schmidt, J. Biol. Chem. **56**, 545 (1923); J. Am. Chem. Soc. **48**, 1709 (1926); Cox, King, and Berg, J. Biol. Chem. **81**, 755 (1929).

III

BENZYL PHTHALIMIDE

$$2C_6H_4(CO)_2NH + 2C_6H_5CH_2Cl + K_2CO_3 \rightarrow$$
$$2C_6H_4(CO)_2NCH_2C_6H_5 + CO_2 + 2KCl + H_2O$$

Submitted by RICHARD H. F. MANSKE.
Checked by HENRY GILMAN and H. J. HARWOOD.

1. Procedure

AN intimate mixture of 166 g. (1.2 moles) of anhydrous potassium carbonate and 294 g. (2 moles) of phthalimide (Note 1) is treated with 506 g. (4 moles) of benzyl chloride (Note 2), and the mixture is heated in an oil bath at 190° under a reflux condenser for three hours (Note 3). While the mixture is still hot, the benzyl chloride is removed by steam distillation (Note 4). Near the end of this operation the benzyl phthalimide crystallizes. It is advisable to cool the mixture rapidly with very vigorous agitation so that the material is in as fine a state of division as possible. The solid is filtered on a large Büchner funnel, thoroughly washed with water, and drained as completely as possible by suction. It is then washed once with 400 cc. of 60 per cent alcohol and drained again. The yield of this product is 340–375 g. (72–79 per cent of the theoretical amount). It is conveniently purified by recrystallizing from hot glacial acetic acid. It then melts at 116° (corr.) (Note 5).

2. Notes

1. The potassium carbonate is conveniently dehydrated by heating in a large basin over a moderate flame. It must be ground to a very fine powder and mixed with the phthalimide in a mortar.

2. A good grade of benzyl chloride having a boiling range of 3° was used.

3. There is no apparent advantage in using mechanical stirring.

4. The excess benzyl chloride is recovered from the distillate and dried with calcium chloride. About 200–300 g. is recovered.

5. The melting point of the crude product is 100–110°, and this is raised to 112.5–113° on crystallization from glacial acetic acid. The recovery on this first crystallization is about 80 per cent.

3. Methods of Preparation

The present procedure is that of Ing and Manske[1] and avoids the troublesome preparation of potassium phthalimide. Diphthalimide-propane and α-bromopropyl phthalimide are conveniently prepared by the same general procedure. In a similar manner, β-phenylethyl bromide gives a 76 per cent yield of β-phenylethyl phthalimide while only a very small amount of styrene is formed in the reaction. The only other feasible preparative method for benzyl phthalimide is from benzyl chloride and potassium phthalimide.[2]

[1] Ing and Manske, J. Chem. Soc. 1926, 2348.
[2] Gabriel, Ber. **20**, 2227 (1887)

IV

p-CHLOROBENZALDEHYDE

$$p\text{-}ClC_6H_4CH_3 + 2Cl_2 \rightarrow p\text{-}ClC_6H_4CHCl_2 + 2HCl$$
$$p\text{-}ClC_6H_4CHCl_2 + 2H_2O \rightarrow p\text{-}ClC_6H_4CHO + 2HCl$$

Submitted by W. L. McEwen.
Checked by Henry Gilman and Chuan Liu.

1. Procedure

A 500-cc. two-neck, round-bottom flask is provided with an air-cooled reflux condenser, 2 cm. in diameter and filled for a length of 60 cm. with 5–6 mm. glass pearls or rings (Note 1). Chlorine is to be introduced by means of a 4-mm. glass tube, inserted through a cork in a neck of the flask, extending close to the bottom of the flask and provided with a small bulb with fine perforations to break up the gas stream into small bubbles. The large quantities of hydrogen chloride formed can be disposed of by means of a gas-absorption trap (Org. Syn. **8**, 27).

Into the tared flask are placed 126.5 g. (1 mole) of p-chlorotoluene (Org. Syn. 3, 34) and 3.8 g. of phosphorus pentachloride. The flask is heated in a bath kept at 160–170° (Note 2), and while illuminated with direct sunlight or with an unfrosted 100-watt tungsten lamp, a rapid stream of chlorine is introduced directly from a cylinder until the gain in weight is 55–66 g. (Note 3).

The pale yellow or yellow-green product is then transferred to a 4-l. wide-mouth bottle containing 400 cc. of concentrated sulfuric acid, and stirred vigorously (Hood) for five hours (Note 4). The viscous mixture is then transferred to a separatory funnel and allowed to stand overnight, after which the lower layer (Note 5) is run slowly, with stirring, into a 3-l. beaker three-quarters filled with cracked ice. The cream-

colored solid obtained when the ice has melted is filtered by suction, washed with water, pressed dry on the funnel and divided into three equal parts. Each portion is dissolved in a minimum of ether, and the ether solution is repeatedly shaken with a 2 per cent sodium hydroxide solution until acidification of the washings gives no precipitate of p-chlorobenzoic acid (Note 6).

After removing the ether by distillation on a steam bath, the residue is distilled under diminished pressure from a Claisen flask. The yield of p-chlorobenzaldehyde distilling at 108–111°/25 mm. and melting at 46–47° is 76–84 g. (54–56 per cent of the theoretical amount).

2. Notes

1. The glass packing reduces the tendency of the stream of hydrogen chloride to carry away p-chlorotoluene as a spray.

If only one run is to be made, good quality corks are satisfactory. If several runs are made, it is recommended that the corks be impregnated with sodium silicate solution to prevent excessive corrosion by the hydrogen chloride and chlorine.

2. The bath contains either oil or graphite.

3. The time required was four and one-half hours. In a larger run by the submitter, in which 750 g. of p-chlorotoluene and 23 g. of phosphorus pentachloride were used, the time required for a gain in weight of 330–360 g. was six to ten hours.

4. Vigorous stirring is necessary to prevent undue foaming. Most of the hydrogen chloride is evolved early in stirring.

5. The waxy upper layer is discarded.

6. The yield of p-chlorobenzoic acid is about 20 g. From the larger runs, starting with 750 g. of p-chlorotoluene, the yield of acid averaged 260 g.

3. Methods of Preparation

p-Chlorobenzaldehyde can be prepared from p-chlorobenzyl chloride or p-chlorobenzyl bromide with aqueous lead nitrate;[1]

[1] Beilstein and Kuhlberg, Ann. **147**, 352 (1867); Jackson and White, Am. Chem. J. **3**, 30 (1881).

from *p*-chlorotoluene and chromyl chloride;[2] by the hydrolysis of *p*-chlorobenzal chloride;[3] from *p*-aminobenzaldehyde by diazotization and subsequent treatment with cuprous chloride;[4] from *p*-chlorophenyl magnesium bromide and ethyl orthoformate;[5] from *p*-chlorobenzyl chloride with hexamethylenetetramine and subsequent hydrolysis;[6] by conversion of *p*-chlorobenzonitrile to the iminochloride which is then hydrolyzed;[7] and by the action of carbon monoxide and aluminum chloride on chlorobenzene.[8]

[2] Law and Perkin, J. Chem. Soc. **93**, 1636 (1908).
[3] Erdmann and Kirchhoff, Ann. **247**, 368 (1888); Erdmann and Schwechten, Ann. **260**, 63 (1890); Kaeswurm, Ber. **19**, 742 (1886).
[4] Von Walther and Raetza, J. prakt. Chem. (2) **65**, 258 (1902).
[5] Bodroux, Bull. soc. chim. (3) **31**, 587 (1904).
[6] Mayer and English, Ann. **417**, 78 (1918).
[7] Stephen, J. Chem. Soc. **127**, 1874 (1925).
[8] Boehringer and Sons, Ger. pat. 281,212 (Chem. Zentr. 1915 (I) 178).

V

DESOXYBENZOIN

$$3C_6H_5CH_2CO_2H + PCl_3 \longrightarrow 3C_6H_5CH_2COCl + H_3PO_3$$

$$C_6H_5CH_2COCl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5CH_2COC_6H_5 + HCl$$

Submitted by C. F. H. ALLEN and W. E. BARKER.
Checked by C. S. MARVEL and TSE-TSING CHU.

1. Procedure

To 68 g. (0.5 mole) of phenylacetic acid (Org. Syn. **2**, 63) (Note 1) in a 1-l. flask fitted with a reflux condenser and a system for absorbing hydrogen chloride (Org. Syn. **8**, 27) (Note 2), is added 35 g. (0.25 mole) of phosphorus trichloride. The mixture is heated on a steam bath for one hour. While the contents of the flask are still warm, 400 cc. of dry benzene is added. The benzene solution of phenylacetyl chloride is decanted from the residue of phosphorous acid on 75 g. (0.56 mole) of anhydrous aluminum chloride in a dry, 1-l. flask which can be fitted to the same condenser. The reaction is vigorous at first and cooling is necessary. The mixture is refluxed for one hour on a steam bath, then cooled and poured into a mixture of 500 g. of cracked ice and 200 g. of concentrated hydrochloric acid. The benzene layer is separated, and the aqueous layer is extracted once with a mixture of 100 cc. of benzene and 100 cc. of ether (Note 2). The ether-benzene solution is washed once with 100 cc. of water (Note 3), and then dried over 40–50 g. of calcium chloride. The solution is filtered (Note 4) with suction into a 1-l. Claisen flask and the solvent is removed by distillation under reduced pressure (Note 5); the residue consists of a brown oil which solidifies on cooling.

The crude material (91–92 g.) is purified by distillation under reduced pressure from a 250-cc. Claisen flask (Note 6). The product distils at 160°/5 mm.; 172°/15 mm.; 200°/30 mm. as a colorless oil which solidifies on cooling. The yield is 81–82 g. (82–83 per cent of the theoretical amount based on the phenylacetic acid used) of a product which melts at 53–54° (Note 7). The product is recrystallized from methyl alcohol, using 4 cc. of solvent for each gram of product (Note 8); the yield is 55–56 g. of crystals melting at 55–56°. An additional 7 g. of crystals melting at 55–56° is obtained by cooling the filtrate in an ice-salt bath. On further cooling of the mother liquors, about 5 g. of crystals melting at 54–55° is obtained. The total yield of purified product is 67–70 g. (Note 9). Further recrystallization of the product from methyl alcohol does not raise the melting point above 55–56°.

2. Notes

1. A very high grade of phenylacetic acid is obtained from companies supplying essential oils and perfumers' supplies.

2. A mixture of benzene and ether is used instead of ether alone because a more efficient separation of the two layers is obtained.

3. Washing with sodium hydroxide at this point is unnecessary and undesirable since, owing to formation of emulsions, it causes an 8–10 per cent loss of product and the product is of no better quality.

4. It is better to remove the calcium chloride by filtration rather than by decantation even though the solution looks clear. Small particles of calcium chloride and aluminum chloride not removed from the solution may cause bumping or even decomposition during the distillation.

5. Removal of the solvent by distillation under reduced pressure on the steam bath makes fractionation unnecessary during distillation of the product.

6. It is necessary to use a Claisen flask with a wide side-arm, since the desoxybenzoin may solidify and clog the apparatus. The distillation under reduced pressure is quiet if directions are followed carefully.

7. The quality of the desoxybenzoin depends upon that of the phenylacetic acid used. In this preparation a high grade of phenylacetic acid was used. The compound prepared according to Org. Syn. **2**, 63, is not so good as some of the commercial products.

8. Methyl alcohol is the best solvent for purification. Desoxybenzoin tends to separate from ethyl alcohol as an oil.

9. Desoxybenzoin is somewhat unstable to light and consequently must be stored in dark bottles.

3. Methods of Preparation

Desoxybenzoin has been prepared by treatment of bromostilbene with water in a sealed tube at 180–190°;[1] by the reduction of benzoin;[2] by the reduction of benzil;[3] by the action of zinc and alcoholic hydrogen chloride on chlorobenzil;[4] by the action of benzene on phenylacetic acid in the presence of phosphorus pentoxide;[5] and by the action of benzene on phenylacetyl chloride in the presence of aluminum chloride.[6]

[1] Limpricht and Schwanert, Ann. **155**, 60 (1870); Kohler and Nygaard, J. Am. Chem. Soc. **52**, 4133 (1930).

[2] Kohler, Am. Chem. J. **36**, 182 (1906); Irvine and Weir, J. Chem. Soc. **91**, 1388 (1907).

[3] Japp and Klingemann, J. Chem. Soc. **63**, 770 (1893).

[4] Thiele and Straus, Ann. **318**, 163 (1901).

[5] Zincke, Ber. **9**, 1771 (1876).

[6] Graebe and Bungener, Ber. **12**, 1080 (1879).

VI

DESYL CHLORIDE

$$C_6H_5CHOHCOC_6H_5 + SOCl_2 \rightarrow C_6H_5CHClCOC_6H_5 + SO_2 + HCl$$

Submitted by A. M. WARD.
Checked by C. S. MARVEL and TSE-TSING CHU.

1. Procedure

IN a 1-l. beaker are placed 100 g. (0.47 mole) of benzoin (Org. Syn. 1, 33), and 50 g. of pyridine. The mixture is heated until a solution is obtained, then cooled in an ice bath until solid. The mass is coarsely ground, and 75 g. (0.63 mole) of thionyl chloride is added slowly with vigorous stirring and cooling in a water bath. After each addition of thionyl chloride, the reaction mixture becomes quite hot, and considerable amounts of sulfur dioxide and hydrogen chloride are evolved. At first the mass becomes pasty and then soon sets to a light yellow solid. After about an hour, water is added and the solid is coarsely ground and filtered. It is finely triturated twice with water, filtered by suction, and pressed as dry as possible. The white powder is dried to constant weight over sulfuric acid or calcium chloride. The yield of crude product is about 125 g. The compound is dissolved in 450 cc. of boiling 95 per cent alcohol (Note 1), filtered, and the filtrate cooled by running water. There is obtained 77 g. of colorless crystals, which, after drying in the air, melt at 66–67°. On cooling the mother liquor in an ice-salt mixture, there is obtained an additional 9 g. of crystals melting at 65–66°. Further cooling of the filtrate yields no more product. The total yield is 80–86 g. (75–79 per cent of the theoretical amount) (Notes 2 and 3).

2. Notes

1. The product may be recrystallized from petroleum ether (b.p. 40–60°), but this solvent is less satisfactory for large amounts of material.

2. When the preparation is carried out with one-fifth these quantities the yield is only about 70 per cent of the theoretical amount.

3. Desyl chloride decomposes and becomes brown when exposed to sunlight, but is quite stable if kept in dark bottles.

3. Methods of Preparation

Desyl chloride has been prepared by the action of thionyl chloride on benzoin,[1] and on *l*-benzoin.[2] It has also been prepared by the action of hydrogen chloride on azibenzil.[3]

[1] Schroeter, Ber. **42**, 2348 (1909).
[2] McKenzie and Wren, J. Chem. Soc. **97**, 481 (1910).
[3] Curtius and Lang, J. prakt. Chem. **44**, 547 (1891).

VII

DIBENZALACETONE

$$2C_6H_5CHO + CH_3COCH_3 \rightarrow C_6H_5CH{=}CH{-}CO{-}CH{=}CHC_6H_5 + 2H_2O$$

Submitted by Charles R. Conrad and Morris A. Dolliver.
Checked by H. Lohse and C. R. Noller.

1. Procedure

A cooled solution of 100 g. of sodium hydroxide in 1 l. of water and 800 cc. of alcohol (Note 1) is placed in a 2-l. wide-mouth glass jar which is surrounded with water and fitted with a mechanical stirrer. The temperature of the solution is kept about 20–25° (Note 2). This solution is stirred vigorously (Note 3), and one-half of a mixture of 106 g. (1 mole) of benzaldehyde (Note 4) and 29 g. (0.5 mole) of acetone (Note 4) is added. In about two or three minutes a yellow cloud forms which soon becomes a flocculent precipitate. After fifteen minutes the rest of the mixed reagents is added, and the container is rinsed with a little alcohol which is added to the mixture. Vigorous stirring is continued for one-half hour longer and the mush then filtered with suction on a large Büchner funnel. The product is thoroughly washed with distilled water (Note 5) and then dried at room temperature to constant weight. The yield is 105–110 g. (90–94 per cent of the theoretical amount) (Note 6). The product contains a little sodium carbonate and melts at 104–107°.

The crude dibenzal acetone may be recrystallized from hot ethyl acetate, using 100 cc. of solvent for each 40 g. of material. About 80 per cent of the material is recovered melting at 110–111°.

2. Notes

1. Sufficient alcohol is used to dissolve the benzaldehyde rapidly, as well as to retain the benzalacetone in solution until it has had time to react with the second molecule of aldehyde. Lower concentrations of base slow up the formation of the dibenzalacetone and thus favor side reactions which tend to yield a sticky product. Higher concentrations of base give added difficulty in washing. These concentrations were suggested by, and are approximately the same as, those used in the preparation of benzalacetophenone described in Org. Syn. **7**, 1.

2. Only temperatures between 20 and 25° were tried, it being expected that a change of temperature would have the same effect as it does in the preparation of benzalacetophenone mentioned above.

3. Stirring is essential, as it makes considerable difference in the uniformity of the product.

4. The benzaldehyde was U.S.P. quality which had been washed with sodium carbonate solution and distilled. Commercial C.P. acetone was used. The theoretical quantities are used, since an excess of benzaldehyde results in a sticky product, and an excess of acetone favors the production of benzalacetone. The mixture is prepared before addition in order to insure additions of equivalent quantities.

5. Since the product is practically insoluble in water, large amounts can be used in the washing. Sodium compounds are probably the chief impurities. The dried product contains some sodium carbonate which results from the failure to completely remove the sodium hydroxide. There remain also the impurities insoluble in water. However, the product is pure enough for use in most reactions.

6. If the mush is allowed to stand several hours, chilled, and filtered cold, a slightly larger yield is obtained, but this is not worth while. The filtrate may be used as a medium for a second run in which about 93 per cent of the theoretical yield is obtained. The melting point of the second product is slightly lower.

3. Methods of Preparation

Dibenzalacetone has been prepared by condensing benzaldehyde with acetone using as condensing agents dry hydrogen chloride,[1] 10 per cent sodium hydroxide solution,[2] and glacial acetic acid with sulfuric acid.[3] It has also been obtained by condensing benzalacetone with benzaldehyde in the presence of dilute sodium hydroxide.[4] Straus and Ecker [5] were the first to record the use of ethyl acetate for crystallization.

[1] Claisen and Claparede, Ber. **14**, 350 (1881).

[2] Schmidt, Ber. **14**, 1460 (1881); Claisen, ibid. **14**, 2470 (1881); Straus and Caspari, ibid. **40**, 2698 (1907).

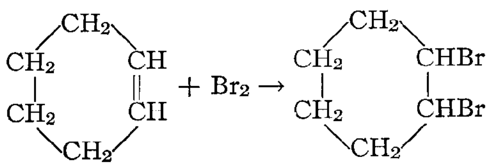
[3] Claisen and Claparede, Ber. **14**, 2460 (1881).

[4] Claisen and Ponder, Ann. **223**, 141 (1884).

[5] Straus and Ecker, Ber. **39**, 2988 (1906).

VIII

1,2-DIBROMOCYCLOHEXANE



Submitted by Harry Greengard.
Checked by C. S. Marvel and J. Harmon.

1. Procedure

In a 3-l. three-neck round-bottom flask fitted with a 500-cc. separatory funnel, a mechanical stirrer, and a thermometer, is placed a solution of 123 g. (1.5 moles) of cyclohexene (Note 1) (Org. Syn. **5**, 33) in 300 cc. of carbon tetrachloride. The flask is surrounded by an ice-salt bath. The entire apparatus is assembled in direct sunlight (Note 2). The stirrer is started, and when the temperature has reached 0° a solution of 210 g. (1.31 moles) of bromine in 145 cc. of carbon tetrachloride is added from the separatory funnel at such a rate that the temperature of the reaction mixture does not exceed 3° (Note 3). The addition requires about two hours.

When the addition of the bromine is complete, the flask is attached to a condenser set for distillation, and the carbon tetrachloride and excess cyclohexene are distilled from a water bath (Notes 4 and 5). The dark-colored residue is transferred to a 500-cc. modified Claisen flask (Org. Syn. **1**, 40) and distilled under reduced pressure. There is a small low-boiling fraction, and then pure dibromocyclohexane distils at 108–112°/25 mm. The yield is 238–281 g. (73–86 per cent of the theoretical amount) (Notes 6 and 7).

2. Notes

1. The cyclohexene boiled over a two-degree range. The yield was consistently better when cyclohexene boiling over a one-degree range was used, but the increased yield did not compensate for the loss in the purification of the cyclohexene.

2. When the reaction was run in the dark or on very cloudy days the yield dropped to about 60 per cent of the theoretical amount.

3. Unless the temperature is controlled carefully, the yield is poor because of substitution reactions. Even at this low temperature some substitution occurs unless the excess of cyclohexene is used.

4. The dibromide decomposes on continued exposure to the air and becomes very dark. Hence the product should be distilled at once.

5. The distillate contains a trace of the dibromide, as shown by the fact that it darkens on exposure to the air.

6. The product is stored best in sealed bottles with as little exposure to the air as possible. The product which has stood for some time can be purified by redistillation with a loss of 10–25 per cent.

7. The residue in the distilling flask is rather oily and adheres to the glass. It is removed best by boiling with concentrated sodium hydroxide solution.

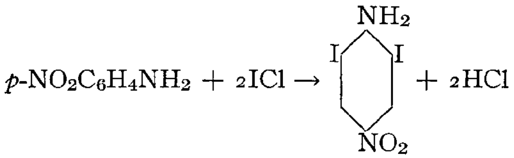
3. Methods of Preparation

1,2-Dibromocyclohexane has been prepared by the treatment of cyclohexene with bromine in solution in chloroform,[1] ether,[2] and aqueous sodium bromide.[3]

[1] Baeyer, Ann. **278**, 108 (1894); Hoffmann and Damm, Mitt. schlesischen Kohlenforsch. Kaiser Wilhelm Ges. **2**, 97 (1925), (C. A. **22**, 1249 [1928]).
[2] Fortey, J. Chem. Soc. **73**, 948 (1898).
[3] Markownikoff, Ann. **302**, 29 (1898).

IX

2,6-DIIODO-*p*-NITROANILINE



Submitted by R. B. Sandin, W. V. Drake, and Frank Leger.
Checked by Frank C. Whitmore and Marion M. Whitmore.

1. Procedure

One hundred thirty-eight grams (1 mole) of *p*-nitroaniline (Eastman Technical grade) is dissolved in 370 cc. of boiling glacial acetic acid in a 2-l. three-neck flask provided with a mechanical stirrer, a reflux condenser and a dropping funnel. The burner is removed and a mixture of 325 g. (2 moles) of iodine monochloride (Note 1) in 100 cc. of glacial acetic acid is added slowly from the dropping funnel with rapid stirring during thirty minutes. Considerable heat is evolved. The mixture is heated on a rapidly boiling water bath for two hours and then transferred to a 1-l. beaker and allowed to cool. The solidified mixture is treated with 100 cc. of glacial acetic acid. Any hard lumps are crushed thoroughly with a flat glass stopper (Note 2). The mixture is transferred to a large Büchner funnel and filtered by suction, two 25-cc. portions of glacial acetic acid being used to wash the last of the crystals into the funnel. The dark mother liquor is removed as much as possible by suction. The crystals are returned to the beaker, thoroughly stirred with 200 cc. of cold glacial acetic acid and transferred to the suction filter again. The beaker is rinsed with two 25-cc. portions of

glacial acetic acid, and the crystals are sucked as dry as possible. The suction is shut off, and the crystals are wetted with 50 cc. of ether. The suction is again used to remove the ether. The product is air dried to constant weight (about 24 hours). The yield of air-dried diiodo-*p*-nitroaniline melting at 243–245° (uncorr.) is 220–250 g. (78–89 per cent of the theoretical amount).

2. Notes

1. The iodine monochloride is made by passing dry chlorine gas into 254 g. (1 mole) of iodine in a tared 500-cc. Erlenmeyer flask until the gain in weight is 71 g. Frequent shaking is necessary. The iodine monochloride is used directly without distillation.

2. It is advisable to wear rubber gloves during these operations with glacial acetic acid.

3. Methods of Preparation

2,6-Diiodo-*p*-nitroaniline has been made by the action of iodine chloride on a chloroform solution [1] and also on a glacial acetic acid solution [2] of *p*-nitroaniline.

[1] Michael and Norton, Ber. **11**, 113 (1878).
[2] Willgerodt and Arnold, Ber. **34**, 3344 (1901).

X

2,4-DINITROBENZALDEHYDE

$$C_6H_5N(CH_3)_2 + 2HCl + NaNO_2 \rightarrow ONC_6H_4N(CH_3)_2 \cdot HCl + NaCl + H_2O$$

$$ONC_6H_4N(CH_3)_2 \cdot HCl + CH_3C_6H_3(NO_2)_2 + Na_2CO_3 \rightarrow (CH_3)_2NC_6H_4N{=}CHC_6H_3(NO_2)_2 + NaCl + NaHCO_3 + H_2O$$

$$(CH_3)_2NC_6H_4N{=}CHC_6H_3(NO_2)_2 + H_2O + HCl \rightarrow C_6H_3(NO_2)_2CHO + (CH_3)_2NC_6H_4NH_2 \cdot HCl$$

Submitted by G. M. BENNETT and E. V. BELL.
Checked by J. B. CONANT and R. E. SCHULTZ.

1. Procedure

A SOLUTION of 300 g. (2.4 moles) of technical dimethyl aniline in 1050 cc. of concentrated hydrochloric acid is placed in a large jar or crock and finely divided ice added until the temperature has fallen to 5°. The contents of the jar are then stirred mechanically, and a solution of 180 g. (2.6 moles) of sodium nitrite in 300 cc. of water is slowly added from a separating funnel, the stem of which dips beneath the surface of the liquid. The addition takes one hour, and the temperature is kept below 8° by the addition of ice if necessary. When all the nitrite has been added the mixture is allowed to stand one hour and then filtered. The solid *p*-nitrosodimethylaniline hydrochloride is washed with 400 cc. of 1 : 1 hydrochloric acid and then with 100 cc. of alcohol. After drying in air, it weighs 370–410 g. (80-90 per cent of the theoretical amount).

In a 3-l. flask a mixture of 330 g. (1.7 moles) of air-dried

p-nitrosodimethylaniline hydrochloride (Note 1) with 100 g. of anhydrous sodium carbonate and 1.5 l. of 95 per cent alcohol is heated on the steam bath for thirty minutes and filtered to remove sodium chloride and unchanged carbonate. The filtrate is placed with 300 g. (1.6 moles) of 2,4-dinitrotoluene (m.p. 70°) in a 5-l. flask provided with a mechanical stirrer and a reflux condenser and heated on the steam bath with stirring for five hours. When the contents of the flask are cold, the condensation product is collected on a Büchner funnel and well drained by means of a suction pump and a piece of "rubber dam" (Note 2) fastened over the top of the funnel. The rubber is drawn down onto the solid by the suction, thus forcing the liquid out. The dark green solid is washed by transferring it to a large beaker, stirring it with 1 l. of 95 per cent alcohol on the steam bath for half an hour, cooling and filtering again, using the rubber dam. The dinitrobenzylidene-*p*-aminodimethylaniline is placed while still damp in a large round-bottom flask containing 500 cc. of a mixture of equal volumes of concentrated hydrochloric acid and water, and steam is blown in by a tube reaching to the lowest part of the vessel. Vigorous injection of steam is continued for fifteen minutes after the liquid has reached a temperature of 105° C. (Note 3).

When cold the aqueous layer is decanted (or filtered) from the solidified product and the process of steam-agitation with acid is repeated, another 500 cc. of dilute acid being added (Note 4). Finally the solid is filtered off, washed with water and dried in vacuo. The crude dinitrobenzaldehyde so obtained weighs 170–210 g. and melts at 40–50°. It is purified by heating in two lots each with 8 l. of naphtha (b.p. 90–110°) in a large flask on the steam bath with mechanical stirring for three hours, decanting the solution (temperature of liquid 80°) and allowing to crystallize. The purified dinitrobenzaldehyde, air-dried, weighs 79–104 g. (24–32 per cent of the theoretical amount) and melts at 69–71° (Note 5). From the mother liquors, impure material may be recovered by evaporation or by distillation in steam, from which by a similar process of crystallization a further 20 g. of aldehyde of m.p. 66° can be separated.

2. Notes

1. Attempts to use technical nitrosodimethylaniline in place of the freshly prepared material were not successful.

2. This is the type of thin rubber used by dentists.

3. It is essential that the temperature reach the maximum (about 105°) and be kept at this point for sufficient time during the hydrolysis.

4. The acid aqueous liquors contain *p*-aminodimethylaniline and might be utilized in the preparation of quinoneimine dyes.

5. 2,4-Dinitrobenzaldehyde is a useful reagent in that it forms highly crystalline condensation products with (*a*) amines, (*b*) substances having a reactive methylene or methyl group.[1]

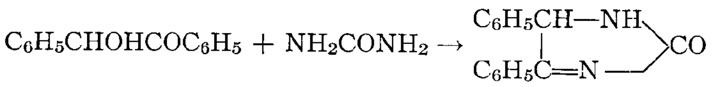
3. Methods of Preparation

Dinitrobenzaldehyde was first prepared from dinitrotoluene.[1,2,3] It has also been prepared from 2,4-dinitrobenzylaniline,[4,5] and from dinitrobenzyl alcohol.[5]

1 Bennett and Pratt, J. Chem. Soc., 1929, 1465.
2 Sachs and Kempf, Ber. **35**, 1224 (1902); D.R.P. 121745.
3 Muller, Ber. **42**, 3695 (1909).
4 Sachs and Everding, Ber. **35**, 1237 (1902).
5 Cohn and Friedlander, Ber. **35**, 1266 (1902).

XI

4,5-DIPHENYLGLYOXALONE



Submitted by B. B. Corson and Emeline Freeborn.
Checked by Frank C. Whitmore and Marion M. Whitmore.

1. Procedure

A MIXTURE of 212 g. (1 mole) of benzoin (Note 1), 110 g. (1.85 moles) of urea and 800 cc. of glacial acetic acid in a 2-l. round-bottom flask is heated under a reflux condenser for seven hours (Note 2). The hot solution is quickly poured into a 2-l. beaker (Note 3) and allowed to stand at least three hours. The cold mixture is transferred by means of a large wooden spoon or spatula to a 30-cm. Büchner funnel and sucked as dry as possible (see p. 31). The crystals are pressed down during the suction filtration. The filtrate is discarded. The crystals are returned to the beaker, stirred mechanically with 500 cc. of ether for thirty minutes and filtered again by suction (Note 4). The crystals are spread out and allowed to dry at least overnight (Note 5). The product is heated with 1 l. of glacial acetic acid in a 2-l. round-bottom flask attached to a reflux condenser (Note 6). The clear solution is poured with mechanical stirring into 2500 cc. of water in a 4-l. (1-gal.) crock. The stirring is continued for thirty minutes (Note 7). The mixture is filtered on a 30-cm. Büchner funnel and pressed and sucked as dry as possible. The crystals are transferred to the 2-l. beaker and stirred mechanically for ten minutes with 1 l. of water. After filtration, the washing with water is repeated. The

crystals are then returned to the beaker, stirred with 750 cc. of ether and filtered again. The product is then air dried to constant weight. The yield of white fluffy crystals of diphenylglyoxalone melting at 330–335° (corr.) (Note 8) is 220–230 g. (92–97 per cent of the theoretical amount).

2. Notes

1. The benzoin (Org. Syn. **1**, 33) need not be recrystallized.
2. At first the color is reddish orange but later it changes to dark yellow.
3. If left in the flask it solidifies too much to be removed readily.
4. Unreacted benzoin is removed by the ether in which diphenylglyoxalone is only sparingly soluble.
5. The product is difficult to dry completely.
6. This step is not successful if less than 1 l. of glacial acetic acid is used.
7. The water removes any unreacted urea.
8. The melting point is conveniently taken on the surface of mercury heated in a test tube with the thermometer dipping in the mercury.

3. Methods of Preparation

The only method of preparative interest is the interaction between benzoin and urea in acetic acid solution as described by Biltz[1] and Chattaway.[2]

[1] Biltz, Ann., **368**, 173 (1909).
[2] Chattaway and Coulson, J. Chem. Soc. 1928, 1363.

XII

ETHYL α,β-DIBROMO-β-PHENYLPROPIONATE

$$C_6H_5CH{=}CHCO_2C_2H_5 + Br_2 \rightarrow C_6H_5CHBrCHBrCO_2C_2H_5$$

Submitted by T. W. Abbott and Darrell Althousen.
Checked by Henry Gilman and G. F. Wright.

1. Procedure

In a 1-l. round-bottom flask, provided with a two-hole stopper fitted with a dropping funnel and air-vent, is placed 176.2 g. (1 mole) of ethyl cinnamate (Org. Syn. **9**, 38) dissolved in 100 cc. of carbon tetrachloride (Note 1). The flask is placed in ice, and 159.8 g. (51.2 cc., 1 mole) of bromine is added in small quantities with frequent stirring (Note 2).

After standing for one hour, the solution is poured into a large dish and the carbon tetrachloride and unused bromine allowed to evaporate spontaneously (Note 3). The dibromo ester separates in large crystals which form a solid cake in the bottom of the dish (Note 4). This cake is broken up and spread in a thin layer on a large Büchner funnel and subjected to suction until all traces of bromine have disappeared. The white crystals are then dried by pressing between large filter papers. The yield of crude dibromo ester is 280–285 g. (83–87 per cent of the theoretical amount). It melts 65–71°.

If pure ester is desired, it may be obtained by recrystallizing from petroleum ether (b.p. 70–90°), with a yield of 80–85 g. of ester melting at 74–75° from 100 g. of crude product.

2. Notes

1. Carbon tetrachloride is used instead of ether, as the latter produces a very disagreeable lachrymator.

2. The bromine disappears rapidly at first, but more slowly

at the end of the reaction. No hydrogen bromide is evolved. The time of addition is about twenty to twenty-five minutes.

3. This process is rather slow; it may be accelerated by inverting over the dish a large funnel which is connected to a suction pump. In this manner the crystalline cake separates in about two hours.

4. If the reaction is carried out carefully, practically no mother liquor is left. However, if such liquor should remain it will yield, on evaporation, crystals which are impure and must be recrystallized before use.

3. Method of Preparation

Ethyl α,β-dibromo-β-phenylpropionate is prepared by adding bromine to ethyl cinnamate.[1]

[1] Anschütz and Kinnicutt, Ber. **11**, 1220 (1878); Aronstein and Hollemann, ibid. **22**, 1181 (1889); Leighton, Am. Chem. J. **20**, 136 (1898); and Sudborough and Thompson, J. Chem. Soc. **83**, 671 (1903).

XIII

ETHYL-N-METHYLCARBAMATE

$$ClCO_2C_2H_5 + CH_3NH_2 + NaOH \rightarrow CH_3NHCO_2C_2H_5 + NaCl + H_2O$$

Submitted by W. W. Hartman and M. R. Brethen.
Checked by J. B. Conant and C. F. Bailey.

1. Procedure

In a 2-l. flask provided with a mechanical stirrer and cooled by an ice-salt mixture, are placed 300 cc. of ether and 186 g. (2 moles) of a 33 per cent aqueous methylamine solution. When the stirred mixture has cooled to 5°, 217 g. (2 moles) of ethyl chloroformate (Note 1) is added without allowing the temperature to rise above 5°. When almost half of the chloroformate has been added a cold solution of 80 g. (2 moles) of pure sodium hydroxide in 120 cc. of water is added gradually along with the rest of the chloroformate at such a rate that the last of the two solutions are added simultaneously. Constant mechanical stirring throughout the addition is essential. After standing for fifteen minutes the ether layer is separated and the aqueous solution is extracted with 100 cc. of ether. The combined ether layers are rapidly dried by shaking for a short time with about 8 g. of potassium carbonate in two portions. The ether is then distilled and the residue distilled under reduced pressure, the distillate being collected at 55–60°/12 mm. The yield of colorless oil is 182–185 g. (88–90 per cent of the theoretical amount).

2. Notes

1. Technical ethyl chloroformate (chlorocarbonate) is manufactured by the U. S. Industrial Chemical Company.

2. The rate of addition is determined by the efficiency with

which the heat is removed from the reaction mixture. Five hours were required, using an ice-salt mixture outside.

3. Methods of Preparation

Ethyl-*n*-methylcarbamate has been prepared by adding aqueous methylamine to ethyl chloroformate;[1] and from methyl carbamyl chloride and ethyl alcohol.[2]

[1] Schreiner, J. prak. Chem. (2), **21**, 124 (1880); Pechmann, Ber. **28**, 855 (1895).
[2] Gattermann, Ann. **244**, 35 (1888).

XIV

HIPPURIC ACID

$$ClCH_2CO_2H + 2NH_3 \rightarrow NH_2CH_2CO_2H + NH_4Cl$$

$$NH_2CH_2CO_2H + C_6H_5COCl + 2NaOH \rightarrow C_6H_5CONHCH_2CO_2Na + NaCl + 2H_2O$$

$$C_6H_5CONHCH_2CO_2Na + HCl \rightarrow C_6H_5CONHCH_2CO_2H + NaCl$$

Submitted by A. W. INGERSOLL and S. H. Babcock.
Checked by ROGER ADAMS and B. H. WOJCIK.

1. Procedure

To 3 l. (approx. 45 moles) of concentrated ammonium hydroxide (sp. gr. 0.9) (Note 1) in a 5-l. round-bottom flask is added, with shaking, a solution of 95 g. (1 mole) of chloroacetic acid (Note 2) in 100 cc. of water. The flask is stoppered and allowed to stand for four days (Note 3). It is then attached to a condenser for distillation, and the solution is concentrated to 600–700 cc. The excess ammonia is recovered during this process by connecting the lower end of the condenser to a wide tube leading to the bottom of a 3-l. bottle containing 1500 cc. of distilled water and connecting this in the same way with a smaller bottle containing a little water. The bottles are cooled by running water. About 2 l. of 20–23 per cent ammonium hydroxide is recovered in the first receiver (Note 1).

The residual solution is then transferred to a 2-l. beaker, a solution of 50 g. (1.25 moles) of sodium hydroxide in 100 cc. of water and a little decolorizing carbon are added, and the mixture is boiled until the odor of ammonia is completely absent (Note 4). The solution is filtered by suction, diluted to 500 cc.

with water and transferred to a 2-l. round-bottom flask equipped with a mechanical stirrer and cooled by running water. While stirring and cooling below 30°, 150 g. (1 mole) of benzoyl chloride (Note 2) and a cold solution of 80 g. (2 moles) of sodium hydroxide in 200 cc. of water are separately admitted from separatory funnels at such rates that the solution is always only slightly alkaline. About an hour is required for adding the reagents, and the mixture is then stirred for a half hour longer. It is then poured into 125 cc. of concentrated hydrochloric acid in a 2-l. beaker, and after cooling, the precipitate is filtered and dried. The weight at this point is 150–160 g. The solid is placed in a beaker with 300 cc. of technical carbon tetrachloride, the beaker is covered with a watchglass and the mixture is boiled gently for ten minutes. The mixture is then cooled slightly, filtered by gentle suction and the hippuric acid washed on the filter with 50 cc. of carbon tetrachloride (Note 5). After drying, it weighs 135–140 g. For final purification the acid is dissolved in about 2 l. of boiling water, filtered through a steam-heated funnel and allowed to crystallize without artificial cooling. It then appears in characteristic white needles melting at 186–187° (uncorr.). The yield is 115–122 g. (64–68 per cent of the theoretical amount based on the chloroacetic acid used). Upon concentrating the mother liquor to 200 cc., a further 6–7 g. of slightly brown hippuric acid is obtained.

2. Notes

1. An equivalent amount of recovered ammonium hydroxide (sp. gr. 0.93 or less) was used in a number of runs without reducing the yield.
2. Eastman's "Practical" grade reagents were used.
3. The yield was slightly less after two days and no greater after a week.
4. Ammonia must be completely removed to avoid the formation of benzamide.
5. Carbon tetrachloride may be recovered by making the filtrate and washings slightly alkaline with sodium hydroxide, refluxing for a half hour to destroy any benzoyl chloride and

then distilling with steam. Benzoic acid may be recovered by filtering the aqueous residue and acidifying.

3. Methods of Preparation

Hippuric acid has been prepared from the urine of herbivorous animals;[1] by heating benzamide with chloroacetic acid;[2] by heating benzoic anhydride and glycine;[3] by heating benzoic acid and glycine;[4] by heating benzoyl chloride with silver glycinate suspended in benzene;[5] or with glycine and zinc oxide;[6] by the action of benzoyl chloride upon an alkaline solution of glycine.[7]

[1] Gregory, Ann. **63**, 125 (1847); Hallowachs, ibid. **106**, 164 (1858); Henneberg, Stohmann and Rautenberg, ibid. **124**, 200 (1862).

[2] Jazukowitsch, Z. Chem. 1867, 466.

[3] Curtis, Ber. **17**, 1662 (1884).

[4] Dessaignes, Jahresb. 1857, 367.

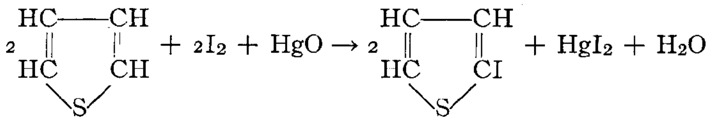
[5] Curtis, J. prakt. Chem. (2), **26**, 145 (1883).

[6] Dessaignes, Ann. **87**, 325 (1853).

[7] Baum, Ber. **19**, 502 (1886); Z. physiol. Chem. **9**, 465 (1895).

XV

IODOTHIOPHENE



Submitted by Wesley Minnis.
Checked by Roger Adams and H. D. Cogan.

1. Procedure

In a glass-stoppered, wide-mouth bottle cooled by ice water are placed 35 g. (0.42 mole) of thiophene (p. 73) and 50 cc. of benzene (Note 1). With constant shaking (Note 2), and cooling when necessary, 75 g. (0.35 mole) of yellow mercuric oxide and 109 g. (0.43 mole) of iodine are added alternately in small amounts during a period of fifteen to twenty minutes. The yellow mercuric oxide changes to crimson mercuric iodide. The mixture is filtered, and the residue is washed with three 25-cc. portions of ether. The ether-benzene filtrate is shaken with a dilute solution of sodium thiosulfate to remove excess iodine and then dried over 5 g. of calcium chloride and filtered. The ether and benzene are removed by distillation on a steam bath (Note 3), and the residue is fractionally distilled under reduced pressure. Iodothiophene distils at 73°/15 mm.; 80–81°/20 mm.; 90–94°/34–38 mm. The yield is 63–66 g. (72–75 per cent of the theoretical amount) (Note 4). If the iodothiophene is still colored by traces of iodine, the color may be removed by shaking with a small amount of mercuric oxide.

2. Notes

1. Ligroin (b.p. 100–120°) may be substituted for benzene.

2. Better yields are obtained when the mixture is vigorously shaken by hand than when mechanical stirring is used. The ordinary stirrer will not keep the mercuric oxide in suspension.

3. Unreacted thiophene can be recovered from the ether-benzene distillate by treating the latter with mercuric oxide and dilute acetic acid, collecting the white precipitate ($C_4H_2S(HgOCOCH_3)HgOH$) on a Büchner funnel, and decomposing it with concentrated hydrochloric acid.[1] In the check preparation there was not enough unreacted thiophene to be recovered.

4. Iodothiophene reacts with magnesium to form a Grignard reagent and is hence useful in the preparation of other thiophene derivatives.

3. Methods of Preparation

Iodothiophene has been prepared only by the action of iodine and mercuric oxide on thiophene.[2]

[1] Dimroth, Ber. **32**, 759 (1899).

[2] Meyer and Kreis, Ber. **17**, 1558 (1884); Thyssen, J. prakt. Chem. (2) **65**, 5 (1902).

XVI

MERCURY DI-β-NAPHTHYL

$$2C_{10}H_7N_2Cl \cdot HgCl_2 + 6Cu \rightarrow (C_{10}H_7)_2Hg + 2N_2 + 6CuCl + Hg$$

Submitted by A. N. Nesmajanow and E. D. Kohn.
Checked by Frank C. Whitmore and R. W. Beattie.

1. Procedure

In a 2-l. round-bottom flask, equipped with a stirrer, are placed 231 g. (0.5 mole) of the addition compound of β-naphthalene diazonium chloride and mercuric chloride (p. 55), 700 cc. of acetone (b.p. 55–57°) and 189 g. (3 moles) of copper powder (Note 1). The mixture is quickly cooled to 20° and stirred for one hour. The mixture is treated with 700 cc. of concentrated aqueous ammonia solution (sp. gr. 0.9), mixed well, and allowed to stand overnight. The supernatant liquid is decanted; the solid is collected on a Büchner funnel and washed successively with 25-cc. portions of water, acetone, and ether. After air-drying, the crude material is recrystallized from xylene, using decolorizing carbon. The crystals thus obtained are slightly yellow (Note 2) and melt at 241.5–243.5°. The yield is 51–55 g. (45–48 per cent of the theoretical amount based on the addition compound used).

2. Notes

1. The same notes apply as in the preparation of β-naphthylmercuric chloride (p. 54).

2. The product of this reaction is never pure white. The treatment of β-naphthylmercuric chloride (p. 55) with sodium iodide, similar to the preparation of mercury di-*p*-tolyl (Org.

Syn. **3**, 65), gives a good yield of a colorless product having the same melting point.[2]

3. Similar results are obtained with other aromatic amines such as aniline and *p*-iodoaniline yielding mercury diphenyl and mercury di-*p*-iodophenyl.

3. Methods of Preparation

Mercury di-β-naphthyl has been prepared by the action of sodium amalgam on β-bromonaphthalene,[1] and by the action of alcoholic sodium iodide on β-naphthylmercuric chloride.[2]

[1] Chattaway, J. Chem. Soc. **65**, 878 (1894); Michaelis, Ber. **27**, 251 (1894).

[2] Private communication, Frank C. Whitmore and R. J. Sobatzki.

XVII

METHYL ISOPROPYL CARBINOL

$$(CH_3)_2CHBr + Mg \rightarrow (CH_3)_2CHMgBr$$

$$(CH_3)_2CHMgBr + CH_3CHO \rightarrow (CH_3)_2CH\cdot CH(OMgBr)CH_3$$

$$(CH_3)_2CHCH(OMgBr)CH_3 + H_2O \rightarrow (CH_3)_2CHCHOHCH_3$$

Submitted by NATHAN L. DRAKE and GILES B. COOKE.
Checked by C. S. MARVEL and B. H. WOJCIK.

1. Procedure

IN a 3-l. three-neck flask fitted with a mechanical stirrer, a separatory funnel, and a reflux condenser, the upper end of which is protected by a calcium chloride tube, are placed 146 g. (6 moles) of dry magnesium turnings (Note 1) and about 250 cc. of dry ether (Note 2).

A solution of 600 g. (4.9 moles) of isopropyl bromide in 300 cc. of dry ether (Note 3) is then added through the separatory funnel. The reaction begins after about 15 cc. of the solution has been added (Note 4). The solution is added at such a rate that the reaction mixture refluxes gently. It is well to arrange for cooling the flask with running water in case the refluxing becomes too vigorous. The addition of the isopropyl bromide solution should require from three and one-half to four hours. The reaction mixture is refluxed on the water bath for forty minutes after addition of the isopropyl bromide solution is complete.

The flask is then cooled to $-5°$ (Note 5), and a solution of 200 g. (4.5 moles) of acetaldehyde (Note 6) in 250 cc. of dry ether is added at this temperature over a period of one hour.

After addition of the acetaldehyde solution is complete, the product is decomposed by pouring the reaction mixture on to 2 kg. of cracked ice. The excess magnesium may be removed conveniently by decantation at this point. The basic magnesium halide is dissolved by addition of about 1 l. of 15 per cent sulfuric acid. The ether solution is separated, and the aqueous layer is extracted with four 150-cc. portions of ether. The ether solutions are combined, dried over 25 g. of calcined potassium carbonate, filtered and fractionally distilled, using a short column. The methyl isopropyl carbinol distils at 110–111.5°. The fraction boiling 37–109° should be dried and refractionated. The total yield is 210–215 g. (53–54 per cent of the theoretical amount) (Note 7).

2. Notes

1. The excess of magnesium is used to increase the yield of Grignard reagent.

2. More ether may be added during the preparation to replace any which may be lost. The ether used should be dried over bright sodium wire.

3. The isopropyl bromide (b.p. 59–60°) was obtained from the Eastman Kodak Company and was used without further treatment.

4. Heating on the water bath to start the reaction should be unnecessary if all the apparatus and reagents are completely dry.

5. The temperature must not be allowed to rise above $-5°$.

6. The acetaldehyde may be prepared conveniently by depolymerizing pure, dry paraldehyde with toluenesulfonic acid as a catalyst. Acetaldehyde boiling at 20.5–21° must be used for this preparation.

7. The yields were no better when gaseous acetaldehyde was used in place of the ether solution.

3. Methods of Preparation

Methyl isopropyl carbinol has been prepared by reduction of methyl isopropyl ketone with sodium amalgam,[1] and with

[1] Münch. Ann. **180**, 339 (1876).

sodium;[2] by treatment of chloroacetyl chloride with zinc methyl;[3] by treatment of bromoacetyl bromide with zinc methyl;[4] by treatment of isobutyraldehyde with methyl magnesium bromide;[5] and as a by-product of the reaction between chloroacetone and methyl magnesium iodide.[6]

[2] Michael and Zeidler, Ann. **385**, 262 (1911).

[3] Bogomolev, J. Russ. Phys.-Chem. Ges. 1, **396** (1881); Ber. **14**, 2066 (1881); Ann. **209**, 86 (1881).

[4] Winogradow, Ann. **191**, 128 (1878).

[5] Henry, Compt. rend. **145**, 22 (1907).

[6] Fourneau and Tiffeneau, Compt. rend. **145**, 438 (1907).

XVIII

S-METHYL ISOTHIOUREA SULFATE

$$2(H_2N)_2CS + (CH_3)_2SO_4 \rightarrow (HN{=}\overset{\overset{\large SCH_3}{|}}{C}{-}NH_2)_2 \cdot H_2SO_4$$

Submitted by P. R. Shildneck and Wallace Windus.
Checked by Henry Gilman and W. F. Schulz.

1. Procedure

In a 2-l. round-bottom flask are mixed 152 g. (2 moles) of finely divided thiourea and 70 cc. of water. To this are added 138 g. (1.1 moles) of technical dimethyl sulfate (poison) (Notes 1 and 2). The flask is immediately attached to a long reflux condenser carrying a trap. The reaction is allowed to progress spontaneously (Note 2) with occasional cooling as the reaction becomes more rapid and the flask becomes filled with vapor. After the initial vigorous reaction is completed, the mixture is refluxed for one hour, during which time crystallization takes place (Note 3). The mixture is then allowed to cool, the flask is removed, 200 cc. of 95 per cent ethyl alcohol is added and the contents of the flask are then filtered with suction. The residue is washed twice with 100-cc. portions of 95 per cent alcohol and allowed to dry in air. The yield is 190 g. of a product which melts with decomposition at 235°. Another crop of crystals weighing 43 g. and melting at 230° can be obtained from the alcoholic filtrate by concentrating it to a paste, to which, after cooling, is added 120 cc. of 95 per cent alcohol. The total yield is 220–233 g. (80–84 per cent of the theoretical amount).

2. Notes

1. Technical dimethyl sulfate, if it has not turned dark brown, need not be distilled before using.

2. If the mixture is cooled too much with ice water, the spontaneous reaction almost ceases and gentle heating must be used to start the reaction again. If the mixture is not cooled, the initial vigorous reaction is so violent that material is likely to be lost through the condenser. Since dimethyl sulfate is poisonous, this must be avoided.

The checkers observed no spontaneous reaction, and in order to initiate reaction the flask and contents were gently heated with a moving low flame. When reaction sets in, the flame is removed. A container with ice water is kept handy to moderate any unduly vigorous reaction, particularly if the water condenser is less than 125 cm. in length.

3. The completion of the vigorous reaction indicates that half of the thiourea is methylated and that the dimethyl sulfate has been converted to methylhydrogen sulfate. Vigorous heating is necessary to compete the methylation.

3. Method of Preparation

The procedure described is essentially that of Arndt.[1]

[1] Arndt, Ber. **54**, 2236 (1921).

XIX

β-NAPHTHYLMERCURIC CHLORIDE

$$C_{10}H_7NH_2 + NaNO_2 + 2HCl + HgCl_2 \rightarrow C_{10}H_7N_2Cl \cdot HgCl_2 + NaCl + 2H_2O$$

$$C_{10}H_7N_2Cl \cdot HgCl_2 + 2Cu \rightarrow C_{10}H_7HgCl + N_2 + 2CuCl$$

Submitted by A. N. Nesmajanow.
Checked by Frank C. Whitmore and R. W. Beattie.

1. Procedure

To 450 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and 500 cc. of water in a 4-l. (1-gal.) earthenware crock equipped with an efficient stirrer is added 143 g. (1 mole) of β-naphthylamine. The suspension of the amine hydrochloride is cooled by the addition of 500 g. of cracked ice. When the temperature reaches 5°, solid sodium nitrite (about 69 g.) is added until starch-iodide paper shows an excess. During the diazotization about 600 g. of cracked ice is introduced at such a rate as to keep the temperature at 5°. The cold solution of the diazonium salt is filtered to remove a small amount of precipitate and returned to the crock. A solution of 271 g. (1 mole) of mercuric chloride in 300 cc. of concentrated hydrochloric acid is mixed with 300 g. of ice and added slowly to the rapidly stirred solution. A heavy yellow solid separates. Stirring is continued for one-half hour to secure complete reaction. The yellow addition compound of β-naphthalene diazonium chloride and mercuric chloride is collected on a 20-cm. Büchner funnel, sucked as dry as possible, and then washed with two 400-cc. portions of water and two 150-cc. portions of acetone (Note 1). The

solid is air dried at about 20° (Note 2) to constant weight. The yield is 380–390 g. (82–85 per cent of the theoretical amount).

In a 2-l. round-bottom Pyrex flask equipped with a stirrer are placed 139 g. (0.3 mole) of the addition compound, 700 cc. of acetone (b.p. 55–57°) (Note 3), and 38 g. (0.6 mole) of copper powder (Note 4). The mixture is cooled at once to about 20°, stirred for one hour, and then allowed to stand overnight. The insoluble material is collected on a Büchner funnel (Note 5). The solid mixture is extracted with about 3 l. of boiling commercial xylene and filtered through a hot funnel. On cooling the filtrate, crystals of β-naphthylmercuric chloride separate (Note 6). The yield of product which melts at 266–267° is 52–64 g. (38–49 per cent of the theoretical amount based on the amine used).

2. Notes

1. The washing with large amounts of solvents is necessary to remove small amounts of highly colored impurities. The product is practically insoluble in the cold wash liquids.
2. The double salt *explodes violently* if heated. On standing a long time even at room temperature it deteriorates slightly. For preparation of the organic mercury compounds the double salt need not be completely dry.
3. Replacement of the acetone by ethyl or methyl alcohol only slightly decreased the yield.
4. The copper powder is prepared from zinc dust and an excess of copper sulfate solution maintained below 70°.
5. The acetone filtrate contains only a trace of the product.
6. The mother liquor from these crystals may be used again to extract the original crude residue, since the product is practically insoluble in cold xylene.
7. If hydrobromic acid and mercuric bromide are used, the product is β-naphthylmercuric bromide.
8. In a similar way, aniline, the three toluidines, and the aminophenols can be converted into the corresponding chloromercuric compounds in about 40 per cent yields.

3. Methods of Preparation

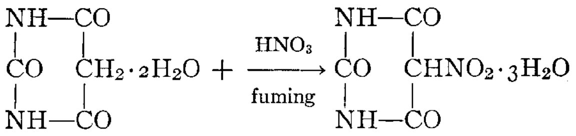
β-Naphthylmercuric chloride has been prepared by the action of mercuric chloride in amyl alcohol on mercury di-β-naphthyl,[1] and from β-naphthalenesulfinic acid and mercuric chloride.[2]

[1] Michaelis, Ber. **27**, 251 (1894).

[2] Whitmore and Howe, "Organic Compounds of Mercury" by F. C. Whitmore, The Chemical Catalog Company, Inc., New York (1921), p. 203.

XX

NITROBARBITURIC ACID



Submitted by W. W. HARTMAN and O. E. SHEPPARD.
Checked by C. S. MARVEL and B. H. WOJCIK.

1. Procedure

IN a 2-l. flask, equipped with a mechanical stirrer and surrounded by an ice bath, is placed 143 cc. of fuming nitric acid (sp. gr. 1.52). Stirring is started and 100 g. (0.61 mole) of barbituric acid is added over a period of two hours; the temperature is kept below 40° during the addition. The mixture is stirred for one hour after the barbituric acid has been added, and stirring is continued while 430 cc. of water is added and the solution is cooled to 10°. The mixture is filtered and the residue is washed with cold water and dried on a glass tray at 60–80° (Note 1). The nitrobarbituric acid is dissolved by adding it to 860 cc. of boiling water in a 2-l. flask and heating the mixture on a boiling water bath while steam is blown in until solution is complete (Note 2). After filtration and cooling overnight, the crystals are removed, washed with cold water, and dried in trays in an oven at 90–95° for two to three hours. The product melts with decomposition at 181–183° when heated rapidly. The yield is 139–141 g. (Note 3). On drying the product at 110–115° for two to three hours, the yield is 90–94 g. (85–90 per cent of the theoretical amount) of an anhydrous compound which melts with decomposition at 176°.

2. Notes

1. Unless the product is dried before recrystallization it is difficult to remove all the nitric acid, and the final product will have a strong odor of nitric acid.

2. If a clear yellow solution is not obtained, decolorizing carbon (Norit) should be added before filtering.

3. This yield is slightly above the theoretical yield of 139 g., but this is probably due to a greater degree of hydration than is indicated in the formula.

3. Methods of Preparation

Nitrobarbituric acid has been prepared by oxidation of violuric acid,[1] and by treatment of barbituric acid with fuming nitric acid.[2]

[1] Ceresole, Ber. **16**, 1134 (1883).
[2] Baeyer, Ann. **130**, 140 (1864).

XXI

PHENYLPROPIOLIC ACID

$$C_6H_5CHBrCHBrCO_2C_2H_5 + 3KOH \rightarrow C_6H_5C{\equiv}CCO_2K + C_2H_5OH + 2KBr + 2H_2O$$

$$C_6H_5C{\equiv}CCO_2K + H_2SO_4 \rightarrow C_6H_5C{\equiv}CCO_2H + KHSO_4$$

Submitted by T. W. Abbott.
Checked by Henry Gilman and G. F. Wright.

1. Procedure

A solution of potassium hydroxide is prepared by dissolving 252.5 g. (4.5 moles) of potassium hydroxide (Note 1) in 1200 cc. of 95 per cent alcohol contained in a 3-l. round-bottom flask provided with a reflux condenser and heated on a steam bath. To the alkaline solution, cooled to 40–50°, is added 336 g. (1 mole) of crude ethyl α,β-dibromo-β-phenylpropionate (p. 37). When the initial reaction has subsided, the contents of the flask are refluxed for five hours on the steam bath.

The reaction mixture is cooled, and the salts which separate are filtered by suction. The filtrate is treated with concentrated hydrochloric acid until neutral (Note 2) to litmus, and the salts which precipitate are separated by filtration. The filtrate is then distilled until the vapor reaches 95°. The residue and the precipitated salts, previously separated by filtration, are combined, dissolved in 800 cc. of water, and chilled by the addition of cracked ice to make a volume of 1800 cc. (Note 3). The cooled solution is immersed in an ice-water bath and stirred mechanically while a 20 per cent sulfuric acid solution is added until the solution is strongly acid to litmus. After stirring for twenty minutes the phenylpropiolic acid is filtered by suction and washed with four 30-cc. portions of a 2 per cent sulfuric acid solution.

The acid thus obtained as a light brown, granular product is dissolved in 1 l. of 5 per cent sodium carbonate solution, treated with 20 g. of decolorizing carbon (Norit), and heated on a steam bath for thirty minutes with occasional stirring. The mixture is then filtered, cooled externally and about 200 g. of cracked ice is added. The solution is stirred mechanically while a 20 per cent solution of sulfuric acid is added slowly. The precipitated acid is filtered by suction, washed first with 50 cc. of a 2 per cent sulfuric acid solution and then with a little water, and air dried. The yield of acid melting between 115–125° is 112–118 g. (76–80 per cent of the theoretical amount).

One hundred grams of the crude acid can be purified by crystallization from 200–300 cc. of carbon tetrachloride, yielding 70 g. of phenylpropiolic acid melting at 135–136°.

2. Notes

1. The best yields are obtained when a 50 per cent excess of potassium hydroxide is used. The concentration of alkali has little or no effect on the yield.

2. The alcohol is best distilled from neutral rather than from from alkaline solution.

3. In order to prevent decarboxylation, the temperature should be kept as low as possible. If this precaution is not observed, the yield is lowered and the product is less pure.

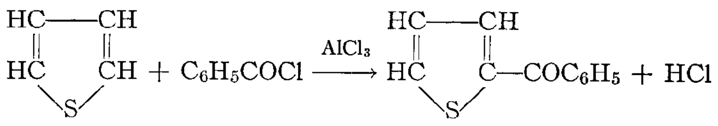
3. Methods of Preparation

The procedure described is essentially that of Perkin.[1] Phenylpropiolic acid can also be prepared from ether solutions of β-bromostyrene [2] and β-chlorostyrene [3] with sodium and carbon dioxide; by the action of alcoholic alkali with α-bromocinnamic acid,[2] β-bromocinnamic acid [4] or ethyl α-bromocinnamate; [5] and by the action of carbon dioxide on sodium phenylacetylide.[6]

[1] Perkin, J. Chem. Soc. **45**, 172 (1884), and Ber. **24**, 4113 (1891).
[2] Glaser, Ann. **154**, 140, 162 (1870).
[3] Erlenmeyer, Ber. **16**, 152 (1883).
[4] Barisch, J. prakt. Chem. (2) **20**, 180 (1879).
[5] Michael, Ber. **34**, 3647 (1902).

XXII

PHENYL THIENYL KETONE



Submitted by Wesley Minnis.
Checked by Roger Adams and H. D. Cogan.

1. Procedure

In a 1-l. three-neck flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer (with bulb immersed in the liquid), are placed 100 g. (0.75 mole) of anhydrous aluminum chloride and 300 g. of carbon disulfide (Note 1). The suspension is cooled to 15–25° and a solution of 60 g. (0.71 mole) of thiophene (p. 72) and 105 g. (0.75 mole) of benzoyl chloride in 225 g. of carbon disulfide is added through the condenser, with stirring, over a period of three and one-half hours (Note 2). The solution is allowed to warm up to room temperature, and stirring is continued for three more hours; the reaction mixture is then allowed to stand overnight. The mixture is refluxed on the water bath for three and one-half hours, cooled, poured on ice, and extracted with ether. The ether extract is washed successively with sodium carbonate solution and water, and then dried over calcium chloride. The ether is removed by distillation on the water bath, and the residue is distilled under reduced pressure. The yield of product boiling at 200–209°/30–40 mm. is 117–120 g. (88–90 per cent of the theoretical amount). On crystallization from 1 l. of petroleum ether (b.p. 65–110°) there is obtained 110–112 g. of product melting at 52°. Another crystallization

from petroleum ether gives a product which melts at 55–56°. The loss on the second crystallization is about 10 per cent.

2. Notes

1. The carbon disulfide was dried over calcium chloride.

2. Thiophene and aluminum chloride react vigorously in carbon disulfide suspension. Subsequent addition of a carbon disulfide solution of benzoyl chloride produces a tar, and a low yield of ketone results.

3. Methods of Preparation

Phenyl thienyl ketone has been prepared by treatment of benzoyl chloride with thienylmercuric chloride;[1] by treatment of thiophene with benzoyl chloride in the presence of thienylmercuric chloride,[2] phosphorus pentoxide,[3] stannic chloride,[4] and aluminum chloride.[5] It has also been prepared from thienylmagnesium iodide and benzonitrile.[6]

[1] Volhard, Ann. **267**, 179 (1892).
[2] Steinkopf and Bauermeister, Ann. **403**, 70 (1914).
[3] Steinkopf, Ann. **413**, 349 (1917).
[4] Stadnikoff and Radowsky, Ber. **61**, 269 (1928).
[5] Comey, Ber. **17**, 790 (1884).
[6] Thomas and Conderc, Bull. soc. chim. (4) **23**, 289 (1918).

XXIII

PROPIONALDEHYDE

$$3CH_3CH_2CH_2OH + K_2Cr_2O_7 + 4H_2SO_4 \rightarrow 3CH_3CH_2CHO + K_2SO_4 + Cr_2(SO_4)_3 + 3H_2O$$

Submitted by CHARLES D. HURD and R. N. MEINERT.
Checked by W. L. MCEWEN and W. H. CAROTHERS.

1. Procedure

ONE HUNDRED grams (125 cc.) (1.6 moles) of *n*-propyl alcohol, b.p. 96–96.6°, is placed in a 2-l. three-neck, round-bottom flask fitted with a mercury-seal stirrer (Note 1), a dropping funnel and a 60-cm. bulb condenser (Note 2) set at an angle of 45°. Water at 60° is kept circulating through this condenser. A condenser set for downward distillation is connected to the top of the first condenser. Cold water circulates through the second condenser. By means of an adapter, the lower end of the latter condenser is fitted to a receiver which is cooled with ice water.

The alcohol in the flask is heated to boiling, stirred, and a mixture of 164 g. (0.56 mole) of potassium bichromate, 120 cc. of concentrated sulfuric acid (2 moles), and 1000 cc. of water is added through the dropping funnel. The addition takes about thirty minutes, and during this time the contents of the flask are kept vigorously boiling. After all the oxidizing mixture has been added, the contents of the flask are boiled for fifteen minutes to distil out the last of the aldehyde. The propionaldehyde which collects in the receiver is dried with 5 g. of anhydrous sodium sulfate and fractionally distilled. The yield of propionaldehyde boiling at 48–55° and having a refractive index of 1.364 (Note 3) is 44–47 g. (45–49 per cent of the calculated amount).

2. Notes

1. The yield of propionaldehyde depends largely upon the efficiency of the stirrer.

2. The purpose of the first condenser is to reflux back to the flask any propyl alcohol which escapes.

3. The recorded value for the index of refraction ($N_D^{20°}$) is 1.3636.

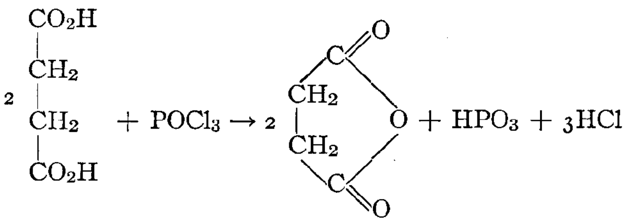
3. Methods of Preparation

Propionaldehye has been prepared by passing propyl alcohol over finely powdered reduced copper;[1] by passing a mixture of propyl alcohol and air over a hot platinum spiral;[2] by dropping propyl alcohol into a bichromate oxidizing mixture;[3] by heating propylene glycol to 500°;[4] by heating a mixture of calcium formate and calcium propionate;[5] by the action of ethyl magnesium iodide on amyl formate;[6] by catalytic hydrogenation of acrolein;[7] by electrolysis of calcium chloride or dilute sulfuric acid solutions of propyl alcohol;[8] by passing vapors of propyl alcohol over cadmium oxide at 325°;[9] by passing vapors of propionic acid and formic acid over titanium oxide at 250–300°;[10] by oxidizing propyl alcohol with a stream of air in the presence of copper bronze, nitrobenzene and quinoline;[11] by treating ethyl orthoformate with ethyl magnesium bromide.[12]

[1] Sabatier and Senderens, Compt. rend. **136**, 923 (1903).
[2] Trillot, Bull. soc. chim. (3) **29**, 38 (1903).
[3] Lieben and Zeisel, Monatsh. **4**, 14 (1883).
[4] Nef, Ann. **335**, 203 (1904).
[5] Linneman, Ann. **161**, 21 (1871).
[6] Centr. (1903) I, 309; DRP 157,573 (1905).
[7] Sabatier and Senderens, Ann. chim. phys. (8) **4**, 398 (1905); (8) **16**, 72 (1909); Skita, Ber. **45**, 3316 (1912).
[8] Reitlinger, Z. elek. Chem. **20**, 261 (1914); Feyer, ibid. **25**, 142 (1919).
[9] Sabatier and Mailhe, Ann. chim. phys. (8) **20**, 303 (1910).
[10] Sabatier and Mailhe, Compt. rend. **154**, 563 (1912).
[11] Rosenberg and Zetzsche, Ber. **54**, 2034 (1921).
[12] Wood and Comley, J. Soc. Chem. Ind. **42**, 431 T (1923).

XXIV

SUCCINIC ANHYDRIDE



Submitted by R. L. Shriner and H. C. Struck.
Checked by C. R. Noller, F. B. Hilmer and J. D. Pickens.

1. Procedure

Two hundred and thirty-six grams (2 moles) of succinic acid (Note 1) and 153.5 g. (1 mole) of phosphorus oxychloride are placed in a 1-l. Claisen flask which is equipped with a reflux condenser, the other openings being stopped with corks. To prevent the escape of fumes into the air, a tube leading to a beaker of water is connected to the open end of the condenser.

The mixture is heated (Note 2) with a free flame for about fifty minutes until no more hydrogen chloride is evolved. The condenser is then removed, and the flask arranged for distillation. A tube leading to the drain is placed on the side-arm of the receiving flask to carry off the vapors. A few cubic centimeters are collected before the temperature rises to 255°, at which temperature the receiver is changed and the succinic anhydride collected from 255–260° (Note 3). The yield of product melting at 118–120° is 164–192 g. (82–96 per cent of the theoretical amount).

The crude succinic anhydride may be recrystallized from acetic anhydride: 50 g. is added to 35 cc. of acetic anhydride, heated until dissolved and then cooled in an ice bath. The crystals are filtered with suction, washed with two 20-cc. por-

tions of cold absolute ether, and rapidly air dried at 40°. The yield is 43.5 g., m.p. 119–120°.

2. Notes

1. Succinic acid having a melting point of 189–190° was used. Less pure material gives a lower-melting product.

2. The reaction foams considerably at the start, hence slow and careful heating is necessary. It is best to heat the flask directly with the flame, making certain that all parts of the mixture are heated about equally.

3. The tarry mass left in the distilling flask may be easily removed by warm dilute sodium hydroxide.

3. Methods of Preparation

A 72 per cent yield of succinic anhydride was obtained by treatment of succinic acid with acetic anhydride according to the method for preparing benzoic anhydride (Org. Syn. **3**, 21).

Succinic anhydride has been obtained by distillation of succinic acid with phosphorus pentachloride, or from benzoyl chloride and sodium succinate.[1] It has been prepared from succinic acid and phosphorus oxychloride or phosphorus pentachloride;[2] by distillation of succinic acid with phosphorus pentoxide;[3] from acetyl chloride and barium succinate, or from succinyl chloride and sodium acetate;[4] from ethyl succinate and benzoyl chloride;[5] from succinic acid and acetyl chloride, or from succinyl chloride and oxalic acid;[6] from succinic acid and succinyl chloride; from succinic acid and acetic anhydride;[7] from succinic acid and acetyl chloride;[8] and from sodium succinate and acetic anhydride.[9]

[1] Gerhardt, Chiozza, Ann. **87**, 293 (1853).
[2] Volhard, Ann. **242**, 150 (1887).
[3] d'Arcet, Ann. chim. (2) **58**, 282 (1885).
[4] Heintz, Jahresb. (1859), 279.
[5] Kraut, Ann. **137**, 254 (1856).
[6] Anschütz, Ann. **226**, 8 (1884).
[7] Anschütz, Ber. **10**, 1883 (1877).
[8] Schulz, Ber. **18**, 2459 (1885).
[9] Oddo, Manuelli, Gazz. chim. ital. **26**, 482 (1896).

XXV

β-THIODIGLYCOL

$$2HOCH_2CH_2Cl + Na_2S \rightarrow HOCH_2CH_2SCH_2CH_2OH + 2NaCl$$

Submitted by E. M. Faber and G. E. Miller.
Checked by W. L. McEwen and W. H. Carothers.

1. Procedure

In a 3-l. round-bottom flask equipped with a mechanical stirrer are placed 1500 g. of 20 per cent ethylene chlorohydrin solution (Note 1) and 750 g. of water. The flask is set in an empty pan of suitable size to serve as a bath in case cooling becomes necessary. With the stirrer in operation, 493 g. of crystalline sodium sulfide containing nine molecules of water of crystallization is added to the chlorohydrin solution at a rate which will maintain the temperature at 30–35°. This will require from forty to sixty minutes. After all the sodium sulfide has been added the solution is stirred for thirty minutes.

The stirrer is removed, and the flask is fitted with a reflux condenser and a thermometer which dips into the liquid. The flask is then heated on a steam bath until the temperature of the liquid is 90°, and for a period of forty-five minutes the temperature is held at 90–95°. The solution is then cooled to 25° and neutralized to turmeric paper by adding concentrated hydrochloric acid drop by drop (Note 2). After filtering, the solution is returned to the flask for concentration at reduced pressure.

The flask is equipped with a short column, attached to which is a condenser set for distillation. A capillary is provided to prevent bumping. The water is then distilled at a pressure of 30–40 mm. by heating the flask in a water bath which is raised to the boiling point as rapidly as is consistent with smooth

distillation. The residue in the flask, which consists of sodium chloride and thiodiglycol, is extracted twice with 500-cc. portions of hot absolute alcohol in order to dissolve the sulfide. After the second extraction, the salt is transferred to a Büchner funnel and is washed with a little hot alcohol (Note 3).

The extract and washings are returned to the distilling flask, and the alcohol is removed under reduced pressure. When practically all the alcohol has distilled, the temperature of the bath is raised to 100° and the residue is heated for three hours under 30-mm. pressure (Note 4).

The crude product which is colorless or very pale yellow weighs 200–215 g. It may be purified by vacuum distillation (Note 5). It boils at 164–166° at 20 mm. The yield of pure material is 180–195 g. (79–86 per cent of the theoretical amount).

2. Notes

1. Aqueous solutions of ethylene chlorohydrin of 18–40 per cent are suitable for the preparation of thiodiglycol; a 20 per cent solution is convenient because the reaction proceeds very smoothly and is easy to control.

In case the chlorohydrin is available in the form of a solution weaker than 20 per cent, it may be concentrated by distillation. Chlorohydrin and water form a constant-boiling-point mixture of 42.5 per cent chlorohydrin which boils at 95.8° at 735 mm.

2. At the end of the reaction the liquid is alkaline and must be neutralized; otherwise considerable decomposition occurs during distillation. Care must be taken not to pass the neutral point, as a small amount of "mustard gas" may be formed. Furthermore, if much acid is present, the heat necessary for vacuum distillation causes resinification and the yield of distilled material falls to about 50 per cent. The use of litmus paper for the neutralization is not satisfactory.

3. If 95 per cent alcohol is used for this extraction, some salt is dissolved with the thiodiglycol. This salt may be filtered off easily after the alcohol has been removed from the product.

4. The time of drying is dependent upon the pressure used.

At 20 mm. the water and alcohol are removed in one hour. If the water has not been completely removed before the alcohol extraction, there may be a small amount of salt left in the material after the alcohol is removed. This may be removed by decanting the product or by pouring it through a glass wool filter.

5. If good-grade chemicals are used in the preparation the crude product is practically water-white and is sufficiently pure for many purposes. A completely pure product can be obtained by vacuum distillation.

3. Methods of Preparation

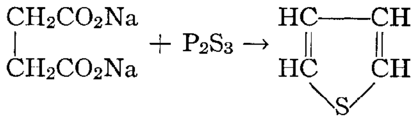
The method described in the procedure is a modification of the one originally described by Meyer.[1] Irvine[2] showed that this general method could be adapted to works-scale production.

[1] Meyer, Ber. **19**, 3260 (1886); Clarke, J. Chem. Soc. **101**, 1582 (1912); Gomberg, J. Am. Chem. Soc. **41**, 1414 (1919).

[2] Irvine, British War Report.

XXVI

THIOPHENE



Submitted by Ross Phillips.
Checked by Roger Adams and H. D. Cogan.

1. Procedure

In a 3-l. round-bottom flask is placed an intimate mixture of 486 g. (3 moles) of finely powdered anhydrous sodium succinate (Note 1) and 648 g. (4.1 moles) of finely ground phosphorus trisulfide (Note 2). The flask is fitted to a 100-cm. (40-in.) condenser set for distillation (Note 3), and a tube for introduction of carbon dioxide is extended through the stopper to the center of the flask. The condenser is connected to a 2-l. flask cooled in an ice-salt mixture. The uncondensed gases are bubbled through two 2-l. flasks connected in series with the receiving flask; each flask is cooled by an ice-salt mixture and contains 1 kg. of cracked ice and 200 cc. of 40 per cent sodium hydroxide.

The reaction flask is thoroughly swept out with carbon dioxide (Note 4), while rotating the flask to remove any air that is trapped by the solid. The flask is then connected to the condenser, and a slow stream of carbon dioxide is passed through the system while the mixture is heated moderately for thirty minutes with a low Bunsen flame (Note 5), and then with the full force of the Bunsen burner until no more yellow vapors are produced (about thirty minutes). Carbon dioxide is passed through more rapidly during the latter heating period to insure complete

removal of the thiophene (Note 6). The contents of the receiver and the two absorption flasks are combined and steam distilled from a 5-l. flask until no more oily drops are formed in the distillate. The thiophene layer in the distillate is separated, dried successively over solid sodium hydroxide and sodium, and fractionated. The yield of product boiling at 83–86° is 63–75 g. (25–30 per cent of the theoretical amount) (Notes 7 and 8).

2. Notes

1. The sodium succinate was prepared from succinic acid, and was dried in shallow pans on a water bath for several days.

2. If phosphorus trisulfide is not obtainable, it may be prepared by the following method developed by A. M. Griswold: An intimate mixture of the calculated amounts of finely powdered sulfur and red phosphorus is placed in an earthenware flower pot, sealed at the bottom with a cork. The pot is imbedded in a bucket of sand, and a heavily weighted cover is held in readiness over the top. A lighted match is dropped into the mixture, the lid is quickly put in place, and the crevices are sealed with sand. The reaction should be carried on out-of-doors as it is extremely vigorous and often gives an excellent display of fireworks. When thoroughly cool, the flower pot is broken and the contents are removed and kept in a tightly stoppered bottle. It is desirable to keep this material for some time before grinding, as the freshly prepared product is not completely crystallized and is difficult to grind.

3. Because of the rapid evolution of a large volume of gas, the tube connecting the flask to the condenser should be about 2 cm. in diameter and all stoppers should fit tightly.

4. If the air is not completely removed before heating the flask, the reaction may take place with explosive violence.

5. The checkers found that continual heating was necessary during this part of the preparation.

6. The stopper should not be removed from the reaction flask until the flask is quite cool, in order to prevent ignition of the excess phosphorus trisulfide on contact with the air. The

hard mass remaining may be softened by treatment with hot water, after which it may be broken up and shaken out.

7. The freshly prepared product often deposits a small amount of a brown precipitate on standing for some time. If this is removed by filtration, no further precipitate is formed.

8. Larger runs have been made successfully, but there is greater danger of a violent reaction.

3. Methods of Preparation

Thiophene is found in small amounts in coal gas and benzene.[1] It has been prepared by passing ethylene or acetylene into boiling sulfur;[2] by passing ethyl sulfide through a hot tube;[3] by passing ethylene or illuminating gas over hot pyrites;[4] by heating succinic anhydride with phosphorus pentasulfide;[5] by treatment of erythritol with phosphorus pentasulfide;[6] by treatment of succinic aldehyde with phosphorus trisulfide;[7] by passing acetylene over pyrites at 300°;[8] by treatment of sodium succinate with phosphorus trisulfide;[9] and by passing acetylene and hydrogen sulfide over bauxite at 320°, or over nickel hydroxide at 300°.[10]

[1] Meyer, Ber. **16**, 1471 (1883); **17**, 2642 (1884).
[2] Meyer and Sandmeyer, Ber. **16**, 2176 (1883).
[3] Kekulé, Ber. **18**, 217 (1885).
[4] Nahnsen, Ber. **18**, 217 (1885).
[5] Volhard and Erdmann, Ber. **18**, 454 (1885).
[6] Paal and Tafel, Ber. **18**, 689 (1885).
[7] Harris, Ber. **34**, 1496 (1901).
[8] Steinkopf and Kirchoff, Ann. **403**, 5 (1914); Ger. Pat. 252,375, C. A. **7**, 538 (1913); Aust. Pat. 72,291, C. A. **11**, 869 (1917); Brit. Pat. 16,810, C. A. **8**, 416 (1914); Steinkopf, Chem. Ztg. **35**, 1098 (1911); J. Soc. Chem. Ind. **30**, 1202 (1911).
[9] Volhard and Erdmann, Ber. **18**, 454 (1885); Friedburg, J. Am. Chem. Soc. **12**, 85 (1890).
[10] U. S. Pat. 1,421,743 (C. A. **16**, 3093 [1922]).

XXVII

THIOSALICYLIC ACID

$$HO_2C—C_6H_4—NH_2 \rightarrow HO_2C—C_6H_4—N_2Cl \rightarrow$$
$$HO_2C—C_6H_4—S—S—C_6H_4—CO_2H \rightarrow HS—C_6H_4—CO_2H$$

Submitted by C. F. H. ALLEN and D. D. MACKAY.
Checked by ROGER ADAMS and A. E. KNAUF.

1. Procedure

IN a 4-l. beaker, 290 cc. of water is heated to boiling and 260 g. (1.08 moles) of crystallized sodium sulfide ($Na_2S \cdot 9H_2O$) and 34 g. of powdered sulfur are dissolved by heating and stirring. A solution of 40 g. of sodium hydroxide in 100 cc. of water is then added and the mixture cooled, first in cold water, and finally by a freezing mixture of ice and salt.

In a 2-l. beaker, set in a freezing mixture and provided with a stirrer and a thermometer for reading temperatures to 0°, are placed 500 cc. of water, 137 g. (1 mole) of anthranilic acid and 200 cc. of concentrated hydrochloric acid; the stirrer is started and the mixture cooled to about 6°. Meanwhile 69 g. (1 mole) of sodium nitrite is dissolved in 280 cc. of hot water and the solution cooled in ice; portions are then placed in a separatory funnel of convenient size, supported in such a way that the lower end of the stem extends beneath the surface of the anthranilic acid solution. When the temperature has fallen to 5°, the nitrite solution is run in, about 500 g. of cracked ice is added at such a rate as to keep the temperature below 5°. This takes about ten minutes (Note 1). A drop of the solution should give an immediate blue color with starch-iodide paper.

The stirrer and thermometer are now transferred to the alkaline sulfide solution, the temperature of which must be

below 5°. The diazo solution is added over a period of twenty to thirty minutes along with 950 g. of ice to prevent a rise above 5°. When addition is complete, the water bath is removed and the mixture allowed to warm up to room temperature; after two hours the evolution of nitrogen ceases (Note 2). About 180 cc. of concentrated hydrochloric acid is added until the solution is acid to Congo red paper, and the precipitate of dithiosalicylic acid is filtered and washed with water.

To remove the excess sulfur, the precipitate is dissolved by boiling with a solution of 60 g. of anhydrous sodium carbonate (soda ash) in 2 l. of water, and the mixture is filtered while hot. It is divided into five equal parts (Note 3) and the dithiosalicylic acid reprecipitated as before with concentrated hydrochloric acid. The solid is filtered, the cake being sucked as dry as possible.

The moist cake is mixed with 27 g. of zinc dust and 300 cc. of glacial acetic acid in a 1-l. round-bottom flask, and the mixture is refluxed vigorously for about four hours (Note 4). When the reduction is complete, the mixture is cooled and filtered with suction. The filter cake is washed once with water and then transferred to a 1-l. beaker. The cake is suspended in 200 cc. of water and the suspension is heated to boiling. The hot solution is made strongly alkaline by the addition of about 40 cc. of 33 per cent aqueous sodium hydroxide solution. The alkaline solution is boiled for about twenty minutes to insure complete extraction of the product from the filter cake, filtered from the insoluble material (Note 5) and the thiosalicylic acid is then precipitated by the addition of sufficient concentrated hydrochloric acid to make the solution acid to Congo red paper. The product is filtered with suction, washed once with water and dried in an oven at 100–110°. The yield of a product which melts at 162–163° is 110–130 g. (71–85 per cent of the theoretical amount based on the anthranilic acid).

This product is sufficiently pure for most purposes (Note 6).

For recrystallization 5 g. of this material is dissolved in 20 cc. of hot 95 per cent alcohol and 40 cc. of water is added. The solution is boiled with a little decolorizing carbon, filtered

hot and then allowed to cool. The product crystallizes in yellow flakes. The yield of recrystallized material is 4.7 g., m.p. 163–164°.

2. Notes

1. This method is much more rapid than when external cooling alone is used (Org. Syn. **2**, 47). The total volume of the solution is not important since the insoluble dithiosalicylic acid is readily filtered.

2. Foaming sometimes becomes very serious during the evolution of nitrogen. The addition of a few cubic centimeters of ether from time to time helps to keep this foaming under control.

3. The dithiosalicylic acid may be precipitated all at once if desired and the entire amount reduced in one operation. If this is done, the reduction must be carried out in a 5-l. flask, fitted with a good stirrer. The mixture needs to be refluxed about ten hours over a ring burner. In the laboratory, this is much less convenient than it is to divide the material and reduce in smaller amounts. The yield is not materially lowered by making the reduction in one portion.

4. The reduction does not always run smoothly, and the zinc sometimes lumps up and becomes inactive. In such cases more zinc must be added. To determine whether reduction is complete, a sample is removed, cooled and filtered. The precipitate is boiled with strong sodium hydroxide solution, filtered and then acidified with hydrochloric acid. If the reduction is complete, the precipitated material will melt at 164° or lower. If the reduction is not complete, the precipitated material will melt above 164°. If the reduction is not complete, the refluxing of the main portion must be continued (and perhaps more zinc must be added) until a test portion shows that the reaction is complete.

In determining the melting point of the material, the capillary tube containing the test sample should be inserted in a bath previously heated to 163–164°.

5. When the reduction is carried out in five portions, one extraction with sodium hydroxide is usually sufficient for each portion. If the reduction is carried out in one operation, several extractions are usually required. When the material is to be extracted more than once, it is best to boil the residue from the first alkaline treatment with hydrochloric acid, filter and then treat again with the alkali.

6. Thiosalicylic acid is used for the preparation of oxythionaphthen and many thioindigoid dyes.

3. Methods of Preparation

Of the several methods described for the production of thiosalicylic acid, only the following are of preparative interest: heating of *o*-halogenated benzoic acids with an alkaline hydrosulfide at 150–200° in the presence of copper or copper salts,[1,5] or by substitution of sodium sulfide at 200°;[2] by reduction of dithiosalicylic acid with glucose,[3] or metals [4,5] in alkaline solution. The dithiosalicylic acid is prepared by treating diazotized anthranilic acid with sodium disulfide in alkaline solution.[4]

[1] (*a*) Ger. Pat. 189,200, C. A., **2**, 609 (1908); (*b*) Cain, "Intermediate Products for Dyes," p. 151.

[2] Ger. Pat. 193,290, C. A., **2**, 1514 (1908); ref. 1 (*b*).

[3] Claasz, Ber. **45**, 2427 (1912).

[4] Ger. Pat. 204,450, C. A., **3**, 1695 (1909); ref. 1 (*b*).

[5] Chem. Age (1929) **21** (p. 11 of Supplement, Aug. 10).

XXVIII

p-TOLUALDEHYDE

$$CO + HCl \xrightarrow{Cu_2Cl_2} HCOCl$$

$$CH_3C_6H_5 + HCOCl \xrightarrow{Al_2Cl_6} p\text{-}CH_3C_6H_4CHO + HCl$$

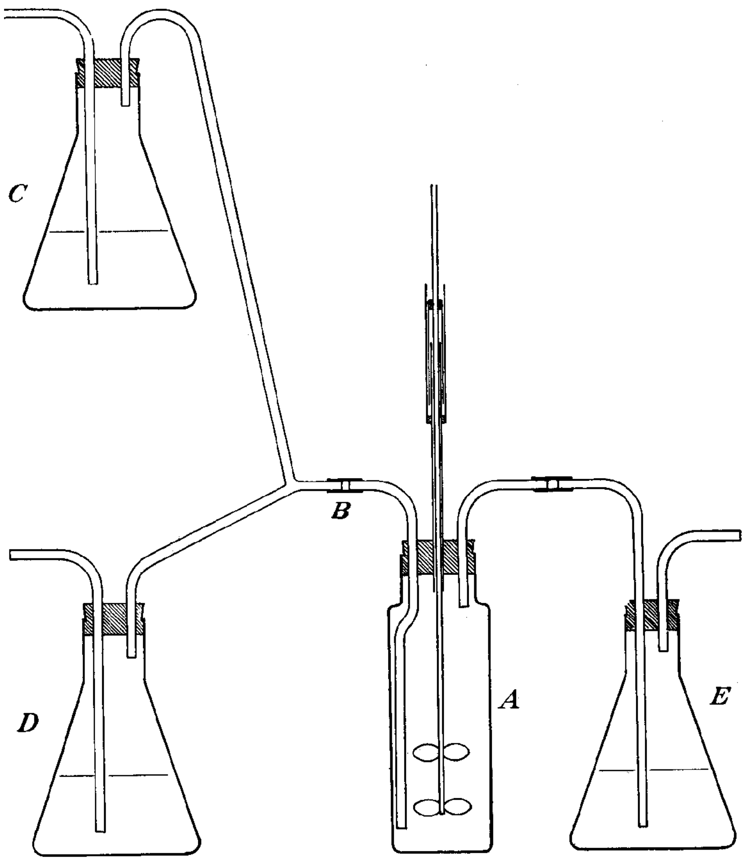
Submitted by G. H. Coleman and David Craig.
Checked by Henry Gilman and J. B. Dickey.

1. Procedure

The apparatus is arranged in a hood, as shown in illustration. The narrow reaction bottle (A), of about 500-cc. capacity and having a wide mouth, is provided with an efficient mercury-sealed mechanical stirrer, an inlet tube (B) for admitting the mixture of gases, and an outlet tube connected with the wash bottle (E). Into (A), contained in a water bath at 20°, is placed 200 g. (2.17 moles) of dry toluene, and then 30 g. (0.15 mole Cu_2Cl_2) of cuprous chloride (Note 1) and 267 g. (2 moles $AlCl_3$) of finely powdered anhydrous aluminum chloride are added rapidly with active stirring.

A mixture of hydrogen chloride (Note 2) and carbon monoxide (Note 3) is led to the bottom of the reaction bottle through tube (B) at such rates that the carbon monoxide is admitted uniformly during seven hours and the hydrogen chloride at about one-half this rate. The rates of flow of the two gases may be compared by the bubbling in wash bottles (C) and (D). The extent of absorption can be estimated from the bubbling of the effluent gases in wash bottle (E). The carbon monoxide is absorbed almost quantitatively at the beginning, and as the mixture thickens the absorption becomes less complete.

The mixture is hydrolyzed by adding it (Note 4) slowly and with shaking to 1.5 kilos of cracked ice in a 3-l. flask. The resulting mixture is then steam distilled until all the aldehyde and unchanged toluene are driven over. After adding 50 cc.



of ether to the distillate, the two layers are separated and the aqueous layer is washed with 150 cc. of ether which is then added to the first non-aqueous layer (Note 5). After drying with calcium chloride, the aldehyde is obtained by distilling from a 500-cc. flask provided with a short fractionating column (Note 6). The yield of p-tolualdehyde distilling at 201–205° is

121–132 g. (50–55 per cent of the theoretical amount based on the toluene). Redistillation involves but a slight loss and gives an almost colorless product which distils at 203–205° (Note 7).

2. Notes

1. The cuprous chloride may be prepared in accordance with Org. Syn. **3**, 33. The mixture is washed several times by decantation with sulfurous acid, filtered on a large Büchner funnel, washed with glacial acetic acid, and dried in an evaporating dish until the odor of acetic acid has disappeared. The cuprous chloride obtained is pure white and should not be exposed unnecessarily to the air.

2. The hydrogen chloride may be generated after the methods used in Org. Syn. **2**, 30, and **8**, 113–114, or in a Kipp generator from fused ammonium chloride and concentrated sulfuric acid.

3. The carbon monoxide may be forced by water from a 75-l. container, after which it is dried by bubbling through two wash bottles containing concentrated sulfuric acid.

In place of this large container for carbon monoxide it is possible to generate the gas more conveniently by adding 170 g. (141 cc.) (3.69 moles) of pure formic acid (sp. gr. 1.2) to 250 g. (135.8 cc.) of concentrated sulfuric contained in a 1-l. distilling flask heated on an oil bath to 70–80°. The side-arm of the flask is connected to the sulfuric acid wash bottles. In order to insure a smooth and constant flow of carbon monoxide, the formic acid is placed in a dropping funnel which extends through a two-hole rubber stopper in the neck of the distilling flask. The other hole of this stopper is connected by rubber tubing to a one-hole stopper in the dropping funnel. No frothing was evident under these conditions, but should frothing occur it is recommended that a small quantity of paraffin be added to the sulfuric acid in the generating flask.

4. The mixture frequently is too thick to be poured, and a spatula must be used to remove it.

5. The extraction of the aldehyde from the unchanged toluene with sodium bisulfite at this point in the preparation does not appreciably increase the purity of the product.

6. It is necessary to use a water-condenser until the temperature reaches 150°, when an air-condenser is used.

7. The use of a few crystals of hydroquinone has been recommended for the storage of *p*-tolualdehyde.

3. Methods of Preparation

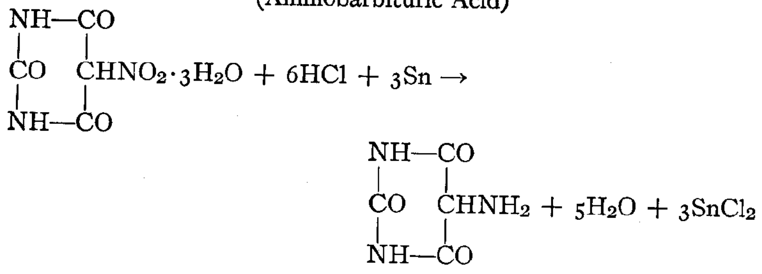
The method described is a modification of that of Gattermann and Koch.[1] The aldehyde has also been prepared by related methods such as the action of hydrogen cyanide and hydrogen chloride on toluene in the presence of aluminum chloride,[2] and nickel carbonyl with toluene and aluminum chloride.[3] The reduction of *p*-tolunitrile by stannous chloride forms the aldimine which on hydrolysis gives an almost quantitative yield of the aldehyde.[4] *p*-Xylene can be oxidized by various reagents, particularly chromyl chloride,[5] to *p*-tolualdehyde.

[1] Gattermann and Koch, Ber. **30**, 1622 (1897).
[2] Friedr. Bayer and Co., D.R.P. 99,568 (1898); Frdl. **5**, 98 (1897–1900).
[3] Dewar and Jones, J. Chem. Soc. **85**, 212 (1904).
[4] Stephen, J. Chem. Soc. **127**, 1874 (1925).
[5] Law and Perkin, J. Chem. Soc. **91**, 258 (1907).

XXIX

URAMIL

(Aminobarbituric Acid)



Submitted by W. W. Hartman and O. E. Sheppard.
Checked by C. S. Marvel and B. H. Wojcik.

1. Procedure

In a 5-l. flask are placed 100 g. (0.44 mole) of nitrobarbituric acid (p. 58) and 600 cc. of concentrated hydrochloric acid, and the mixture is heated on a boiling water bath. To the hot mixture are added 250 g. (2.1 moles) of mossy tin and about 400 cc. of hydrochloric acid over a period of about thirty minutes; heating is continued until there is no yellow color in the liquid (Note 1). The solution is treated with about 3 l. more of concentrated hydrochloric acid, and heated until all the white solid is in solution. Decolorizing carbon (Norit) is added, and the hot mixture is filtered through a sintered-glass funnel (Note 2). The filtrate is allowed to stand in an ice box overnight, and then the precipitate (Note 3) of uramil is collected on a filter and washed with liberal quantities of dilute hydrochloric acid and finally with water (Note 4). The filtrate is concentrated under reduced pressure to about 1 l. and cooled overnight. The additional uramil thus obtained is collected on a Büchner funnel and added to the first product (Notes 5 and 6). The uramil is dried in a desiccator over concentrated sulfuric acid, and finally over

40 per cent sodium hydroxide to remove hydrochloric acid (Note 7).

Uramil is a fine, white powder which becomes pink to red on standing. The yield of a product which does not melt below 400° is 40–46 g. (63–73 per cent of the theoretical amount).

2. Notes

1. Nitrobarbituric acid forms a yellow aqueous solution, but as the color is weak in concentrated hydrochloric acid solution, no trace of it should show at the end of the reaction.

2. If a sintered-glass funnel is not available, the solution may be filtered through a half-inch layer of decolorizing carbon on a double filter paper. After the uramil is once dissolved in the concentrated hydrochloric acid it comes out of solution very slowly, and, if filtered promptly, the solution may be cooled to 60–80° with little loss of product.

3. In occasional runs, the uramil does not crystallize at this point. In this case, the solution should be concentrated and cooled again.

4. Unless the product is washed thoroughly it will contain tin salts.

5. To test for uramil an ammoniacal solution is boiled in the air. A positive test is the appearance of a pink color which gradually grows deeper. The reaction proceeds more rapidly in the presence of mercuric oxide.

6. If the material is dried in the air or in an oven, a pink product is almost always obtained. The pink color is produced more rapidly if ammonia or amines are present in the air.

3. Methods of Preparation

Uramil has been obtained by boiling alloxantin with ammonium chloride;[1] by reduction of nitrosobarbituric acid or nitrobarbituric acid with hydrogen iodide;[2] and by reduction of alloxan phenylhydrazone with tin and hydrochloric acid.[3]

[1] Wöhler and Liebig, Ann. **26**, 310 (1838).
[2] Baeyer, Ann. **127**, 223 (1863).
[3] Kühling, Ber. **31**, 1973 (1898).

XXX

DIETHYL ZINC

$$2C_2H_5I + 2C_2H_5Br + 4Zn \rightarrow 2Zn(C_2H_5)_2 + ZnI_2 + ZnBr_2$$

Submitted by C. R. Noller.
Checked by Henry Gilman, Harriet A. Southgate and C. Mehltretter.

1. Procedure

In a 500-cc. round-bottom flask provided with a reflux condenser (Note 1) and a heavy stirrer (Note 2) is placed 130 g. (approximately 2 gram atoms) of zinc-copper couple (Note 3). To this is added a mixture of 78 g. (0.5 mole) of ethyl iodide and 54.4 g. (0.5 mole) of ethyl bromide (Note 4), the stirrer is started and the mixture heated to refluxing. After one-half hour of refluxing, the reaction starts (Note 5), as is evidenced by the greatly increased rate of refluxing, and the flame is removed. If the reaction becomes too vigorous, the flask is cooled with ice water, but only to the point where the reaction is again under control (Note 6). At the end of one-half hour from the time the flame is removed, the reaction is usually over. The flask is allowed to cool to room temperature (Note 7), connected with a distilling head, condenser and receiver, and distilled under reduced pressure (Note 8) directly from the reaction flask into a 200-cc. round-bottom flask immersed in an ice-salt mixture (Note 9). At the end of the distillation, dry carbon dioxide or purified nitrogen is admitted to the apparatus (Note 10). The yield of crude material, which is sufficiently pure for most purposes, is 53–55 g. (86–89 per cent of the theoretical amount).

For purification, a 30-cm. fractionating column of the Vigreux type is fitted with a condenser and receiving flask provided with

a vent. The extension of this vent is covered with a test tube carrying another small tube for admitting carbon dioxide; the end of the test tube is then loosely plugged by a piece of cotton wool (Note 11). The apparatus is swept out with carbon dioxide, and the receiver containing the crude diethyl zinc is connected to the column. The diethyl zinc is then redistilled at atmospheric pressure (Note 12). The yield of material boiling at 115–120° is 50–52 g. (81–84 per cent of the theoretical amount) (Notes 5 and 13).

2. Notes

1. It is essential that the apparatus be dry and that atmospheric moisture be excluded in order to insure a smooth beginning of the reaction. For this reason, the top of the condenser is either provided with a drying tube containing calcium chloride or attached to a trap [1] to exclude the atmosphere.

2. A slow-moving stirrer that fits the bottom and sides of the flask is necessary in order to keep the zinc thoroughly agitated.

3. The zinc-copper couple may be prepared by either of the following methods:

(*a*) A mixture of 120 g. of zinc dust and 10 g. of powdered copper oxide in a 200-cc. round-bottom flask is heated gently over a free flame in a current of hydrogen with stirring or rotation of the flask until the copper oxide is reduced and a uniform gray mixture is obtained. The temperature should be kept just below the point of fusion during the heating.

(*b*) A zinc-copper alloy containing 5 to 8 per cent copper is prepared by melting zinc with clean brass turnings and casting into bars. This is turned into fine shavings and is ready for use.

When only small quantities of zinc alkyls are to be prepared, method (*a*) may be used to advantage. For large quantities it is believed that the zinc-copper alloy turnings (*b*) are more con-

[1] Gilman and Hewlett, Rec. trav. chim. 48, 1124 (1929).

venient. Zinc-copper couple prepared by method (*a*) must be used at once or stored in an atmosphere of dry inert gas, as it rapidly deteriorates on exposure to moist air.

The method recommended by Noyes[2c] does not seem to yield so active a couple as either of the above methods, and although it gives entirely satisfactory results if pure iodides are used, the yields using a mixture of iodides and bromides are lower.

4. The use of a mixture of alkyl iodide and alkyl bromide is not only less expensive but the reaction is not so vigorous as when the alkyl iodide alone is used.

5. The submitter generally observed that reaction started in twenty to forty minutes after refluxing began. The checkers found that the time for reaction to set in was nearer one and one-quarter hours. Unless all precautions to exclude moisture are exercised, the reaction may not start for several hours. In such cases, after the preliminary period of stirring and heating externally, the mixture can be allowed to stand at room temperature without stirring. Under these conditions the reaction always started spontaneously (in some cases after five hours), and required no attention, for when reaction did set in the refluxing was not sufficiently vigorous to require cooling. When the reaction is slow in starting, the yield of diethyl zinc is somewhat lower.

6. If the mixture is cooled too much, the reaction may stop entirely and is difficult to start again. If this happens the yield will be considerably lower.

7. On cooling, the reaction mass solidifies (probably on account of the re-formation of RZnX) and may be briefly exposed to air without danger. The solid material is much less reactive than diethyl zinc.

8. The pressure should be below 30 mm. of mercury or decomposition will occur.

9. Either a special adapter with a side-arm for applying suction may be used or a piece of right-angled tubing inserted in the same stopper with the condenser tube.

10. When a distillation is carried out under reduced pressure there is no need to sweep out the apparatus with inert gas. At

other times, exposure to air must be prevented by using an atmosphere of carbon dioxide or nitrogen.

The checkers carried out this distillation by heating the flask in an oil bath (about 200°) at a pressure of about 8 mm. The distillation was complete in about one hour. The flask can also be heated directly with a full Bunsen flame.

11. This vent can be replaced by a mercury seal formed by connecting a double right-angled glass tube from the upper part of the receiving flask to a container with mercury. The tube is only slightly immersed in the mercury. When a mercury seal is used, the receiver must be removed when distillation is completed in order to avoid mercury being pulled into the receiver when the system commences to cool.

12. Higher zinc alkyls should be redistilled under reduced pressure.

13. Using the same procedure, the yields and boiling points of higher zinc alkyls are as follows: di-*n*-propyl zinc, 85–86 per cent, b.p. 39–40°/9 mm.; di-*n*-butyl zinc, 78–79 per cent, b.p. 81–82°/9 mm.; di-*iso*-amyl zinc, 50–55 per cent, b.p. 100–103°/12 mm.

3. Methods of Preparation

Diethyl zinc has usually been prepared by the action of ethyl iodide on zinc which has been treated in various ways.[1] The most useful of these zinc preparations are the zinc-copper couples.[2] It has also been prepared from ethyl bromide and zinc-copper couple, using a special catalyst.[3] The above method is essentially the one recently reported.[4] Diethyl zinc has also been prepared by the action of zinc on mercury diethyl.[5]

[1] Frankland, Ann. **85**, 360 (1853).
[2] (*a*) Gladstone and Tribe, J. Chem. Soc., **26**, 445, 678, 961 (1873)
(*b*) Lachman, Am. Chem. J., **19**, 410 (1897); **24**, 31 (1900).
(*c*) Noyes, "Organic Chemistry for the Laboratory," Third edition, p. 61 (1916).
(*d*) Renshaw and Greenlaw, J. Am. Chem. Soc. **42**, 1472 (1920).
[3] Job and Reich, Bull. soc. chim. **33**, 1424 (1923).
[4] Noller, J. Am. Chem. Soc. **51**, 594 (1929).
[5] Frankland and Duppa, J. Chem. Soc. **17**, 31 (1864).

Arylzinc halides, and zinc dialkyls and di-aryls may be prepared by the action of the Grignard reagent on anhydrous zinc chloride in ether solution.[6]

[6] Houben-Weyl, "Methoden der Organischen Chemie," Second edition (1924), Vol. 4, pp. 754, 901; Blaise, Bull. soc. chim. (1911) [4] I–XXVI; Gilman and Brown, J. Am. Chem. Soc. **52**, 4482 (Note 7) (1930).

SUBJECT INDEX

(This Index Comprises Material from Volumes X to XII of this Series)

(Names in small capital letters refer to the titles of preparations which are given in full detail. A number in ordinary bold face type denotes the volume. A number in bold face italics refers to a page which gives preparative directions for a substance formed either as principal product or as a by-product, or to a product which has been prepared by a method analogous to the one given. Other numbers in ordinary type indicate pages on which the compound is mentioned in connection with other preparations.)

A

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VOL. XII

NEW YORK
JOHN WILEY & SONS, INC.
LONDON: CHAPMAN & HALL, LIMITED
1932

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PRINTED IN U. S. A.

PRESS OF
BRAUNWORTH & CO., INC.
BOOK MANUFACTURERS
BROOKLYN, NEW YORK

PREFACE TO VOLUME XII

Since the revised collection of the material in the first nine volumes of this series is soon to appear, no reference to new methods and no corrections for the preparations in these earlier volumes are included here. The index in this volume includes the material in Volumes X and XI but not that in the earlier volumes.

Later References to Preparations in Volumes X and XI

(The numbers in parentheses refer to the volume and page of Organic Syntheses)

Alpha-Aminoisobutyric acid (**11**, 6).

Obtained in 72 per cent yield by using twice the calculated amounts of ammonia and hydrocyanic acid with acetone. Crocker and Lapworth, J. Chem. Soc., **1931**, 1391–1403.

Bromomesitylene (**11**, 24).

When the carbon tetrachloride is distilled off, the oil is likely to turn dark and give off fumes.

Itaconic Acid (**11**, 70).

Produced by a new fungus, "Aspergillus itaconicus." Kinsohita, J. Chem. Soc. Jap. **50**, 583 (1929), C. A. **25**, 5664 (1931).

Triethyl carbinol (**11**, 98).

Obtained by the action of sodium on mixtures of ethyl bromide and diethyl ketone and of ethyl bromide and ethyl propionate in 17 per cent and 9 per cent yields. Morton and Stevens, J. Am. Chem. Soc., **53**, 2244 (1931).

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